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Chubb et al.

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(54) **DIHYDROFURAN AZETIDINE DERIVATIVES
AS ANTIPARASITIC AGENTS**

45/06 (2013.01); C07D 405/14 (2013.01);
C07D 407/10 (2013.01); C07D 407/14
(2013.01); C07D 409/14 (2013.01)

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(56) **References Cited**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

FOREIGN PATENT DOCUMENTS

WO	2008/122375	10/2008
WO	2011/101229	8/2011
WO	2012/017359	2/2012

(21) Appl. No.: **14/375,061**

OTHER PUBLICATIONS

(22) PCT Filed: **Jan. 29, 2013**

PCT International Search Report, PCT/US2013/023662, mailed
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* cited by examiner

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Primary Examiner — Michael Barker

PCT Pub. Date: **Aug. 8, 2013**

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(65) **Prior Publication Data**

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(57) **ABSTRACT**

Related U.S. Application Data

This invention recites dihydrofuran substituted azetidine
derivatives of Formula (1) stereoisomers thereof, veterinarily
acceptable salts thereof, compositions thereof, and their use
as a parasiticide in mammals and birds. The substituents A,
R^{1a}, R^{1b}, R^{1c}, R², R³, R⁴, R⁶, and n are as described herein.

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A61K 31/397 (2006.01)

A61K 31/443 (2006.01)

C07D 405/10 (2006.01)

C07D 409/14 (2006.01)

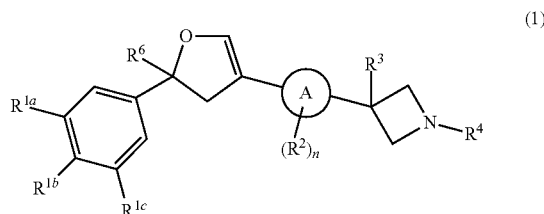
A61K 31/365 (2006.01)

A61K 45/06 (2006.01)

C07D 405/14 (2006.01)

(52) **U.S. Cl.**

CPC **C07D 405/10** (2013.01); **A61K 31/365**
(2013.01); **A61K 31/397** (2013.01); **A61K**



14 Claims, No Drawings

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DIHYDROFURAN AZETIDINE DERIVATIVES AS ANTIPARASITIC AGENTS

FIELD OF THE INVENTION

This invention relates to dihydrofuran aryl azetidine derivatives having parasitocidal activity. The compounds of interest are dihydrofuran derivatives substituted with phenyl-azetidines, naphthyl-azetidines, or heteroaryl azetidines. The invention also relates to compositions and methods of use thereof.

BACKGROUND

There is a need for improved antiparasitic agents for use with mammals, and in particular there is a need for improved insecticides and acaricides. Furthermore there is a need for improved topical and oral products with convenient administration and which contain one or more of such antiparasitic agents which can be used to effectively treat ectoparasites, such as insects (e.g., fleas, lice, and flies) and acarids (e.g., mites and ticks). Such products would be particularly useful for the treatment of companion animals, such as cats, dogs, llamas, and horses, and livestock, such as cattle, bison, swine, sheep, and goats.

The compounds currently available for insecticidal and acaricidal treatment of companion animals and livestock do not always demonstrate good activity, good speed of action, or a long duration of action. Most treatments contain hazardous chemicals that can have serious consequences, including lethality from accidental ingestion. Persons applying these agents are generally advised to limit their exposure. Pet collars and tags have been utilized to overcome some problems, but these are susceptible to chewing, ingestion, and subsequent toxicological affects to the mammal. Thus, current treatments achieve varying degrees of success which depend partly on toxicity, method of administration, and efficacy. Currently, some agents are actually becoming ineffective due to parasitic resistance.

Isoxazoline derivatives have been disclosed in the art as having insecticidal and acaricidal activity. For example, WO2007/105814, WO2008/122375, and WO2009/035004 recite certain alkylene linked amides. Further, WO2007/075459 discloses phenyl isoxazolines substituted with 5- to 6-membered heterocycles. WO2011/101229 discloses certain dihydrofuran derivatives as antiparasitic agents. However, the citations do not exemplify a dihydrofuran substituted phenyl azetidine, nor does the prior art indicate that such compounds would be useful against a spectrum of parasitic species, regardless of morphological lifecycle stages, in animals.

Despite the availability of effective, broad spectrum antiparasitic agents, there remains a need for a safer, convenient, efficacious, and environmentally friendly product that will overcome the ever-present threat of resistance development.

The present invention overcomes one or more of the various disadvantages of, or improves upon, the properties of existing compounds. In particular the present invention develops new isoxazoline substituted phenyl azetidines which demonstrate such properties.

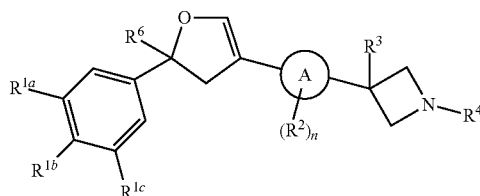
SUMMARY

The present invention provides Formula (1) compounds, stereoisomers thereof, pharmaceutical or veterinarily acceptable salts thereof, which act as parasitocides, in particular, ectoparasitocides; therefore may be used to treat acarids and

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insect infection and infestation in animals. In addition, the invention contemplates the control and prevention endoparasites in animals. The present invention also contemplates the control and treatment of tick borne diseases, for example, Lyme disease, canine and bovine anaplasmosis, canine ehrlichiosis, canine rickettsiosis, canine and bovine babesiosis, epizootic bovine abortion, and theileriosis. Thus, according to the invention, there is provided a compound of Formula (1)

(1)



wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a}, R^{1b}, and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₀-C₃alkylC₃-C₆cycloalkyl, C₁-C₆haloalkoxy, —C(O)NH₂, —SF₅, or —S(O)_pR;

R² is halo, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, nitro, hydroxyl, —C(O)NR^aR^b, C₂-C₆alkenyl, C₂-C₆alkynyl, —S(O)_pR, or —OR;

R³ is hydrogen, halo, hydroxyl, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₀-C₃alkylC₃-C₆cycloalkyl, —C(O)NH₂, nitro, —SC(O)R, —C(O)NR^aR^b, C₀-C₃alkylNR^aR^b, —NR^aNR^bR⁴, —NR^aOR^b, —ONR^aR^b, N₃, —NHR⁴, —OR, or —S(O)_pR;

R⁴ is hydrogen, C₁-C₆alkyl, C₀-C₆alkylC₃-C₆cycloalkyl, —C(O)R⁵, —C(S)R⁵, —C(O)NR^aR⁵, —C(O)C(O)NR^aR⁵, —S(O)_pR^c, —S(O)₂NR^aR⁵, —C(NR⁷)R⁵, —C(NR⁷)NR^aR⁵, C₀-C₆alkylphenyl, C₀-C₆alkylheteroaryl, or C₀-C₆alkylheterocycle;

R⁵ is hydrogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₀-C₆alkylC₃-C₆cycloalkyl, C₀-C₆alkylphenyl, C₀-C₆alkylheteroaryl, or C₀-C₆alkylheterocycle;

R⁶ is cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, —C(O)NR^aR^b, C₂-C₆alkenyl, C₂-C₆alkynyl, C₂-C₆haloalkenyl, or C₂-C₆haloalkynyl;

R⁷ is hydrogen, C₁-C₆alkyl, hydroxyl, cyano, nitro, —S(O)_pR^c, or C₁-C₆alkoxy;

R is C₁-C₆alkyl or C₃-C₆cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C₁-C₆alkyl, or C₀-C₃alkylC₃-C₆cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, C₀-C₃alkylphenyl, C₀-C₃alkylheteroaryl, or C₀-C₃alkylheterocycle, each optionally substituted, where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or —S(O)_pR;

R^c is C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆haloalkylC₃-C₆cycloalkyl, C₀-C₃alkylC₃-C₆cycloalkyl, C₀-C₃alkylphenyl, C₀-C₃alkylheteroaryl, or C₀-C₃alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy,

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C_1-C_6 haloalkyl, $-S(O)_pR$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^b$, $-SCN$, or $-C(O)NR^aR^b$;

each of R^4 and R^5 C_1-C_6 alkyl or C_0-C_6 alkyl C_3-C_6 cycloalkyl can be optionally and independently substituted by at least one substituent selected from C_1-C_6 alkyl, cyano, halo, hydroxyl, C_1-C_6 hydroxyalkyl, oxo, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-S(O)_pR^c$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^c$, $-SCN$, or $-C(O)NR^aR^b$; and

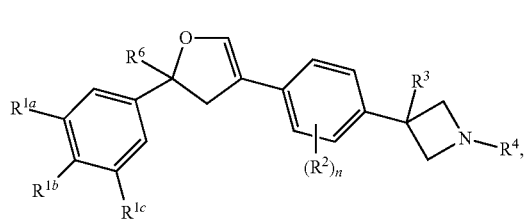
wherein R^4 and R^5 C_0-C_6 alkylphenyl, C_0-C_6 alkylheteroaryl, or C_0-C_6 alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from C_1-C_6 alkyl, cyano, halo, oxo, $=S$, $=NR^7$, hydroxyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-SH$, $-S(O)_pR$, and C_1-C_6 haloalkoxy;

n is the integer 0, 1, or 2, and when n is 2, each R^2 may be identical or different from each other; and

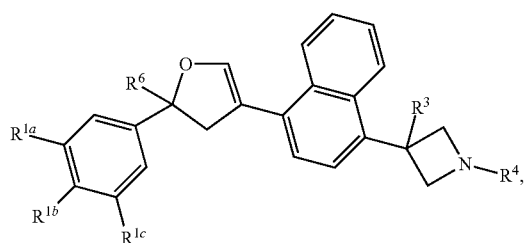
p is the integer 0, 1, or 2; stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazolyl, imidazolyl pyrrolyl, furanyl, thiophenyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, benzofuranyl, benzothiophenyl, indolyl, benzimidazolyl, indazolyl, benzotriazolyl, thieno[2,3-*c*]pyridine, thieno[3,2-*b*]pyridine, and benzo[1,2,5]thiadiazole. In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, benzofuranyl, benzothiophenyl, indolyl, and benzo[1,2,5]thiadiazole. In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, pyrazolyl, and benzo[1,2,5]thiadiazole. In another aspect of the invention, A is phenyl, pyridinyl, naphthyl, or benzo[1,2,5]thiadiazole. In another aspect of the invention A is phenyl or pyridinyl. In another aspect of the invention A is phenyl. In another aspect of the invention A is pyridinyl. In another aspect of the invention, A is naphthyl. In yet another aspect of the invention, A is benzo[1,2,5]thiadiazole.

In another aspect of the invention are compounds of Formula (2), (3), (4), (5), and (6)



(2)

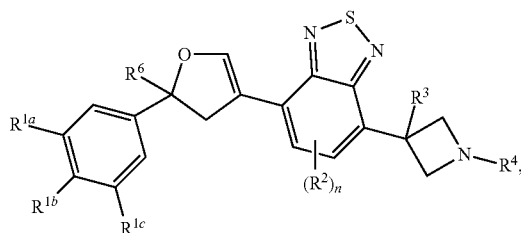


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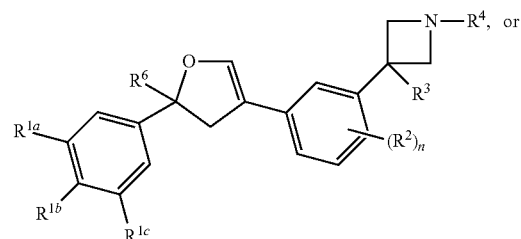
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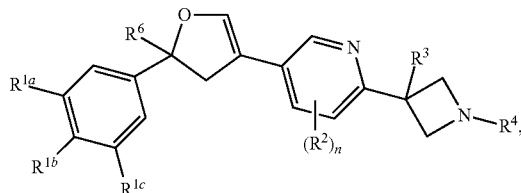


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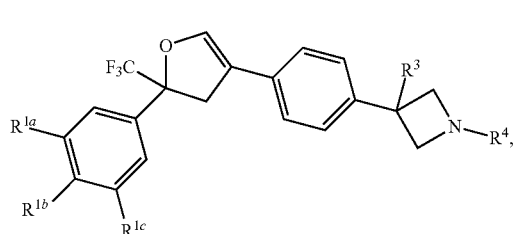
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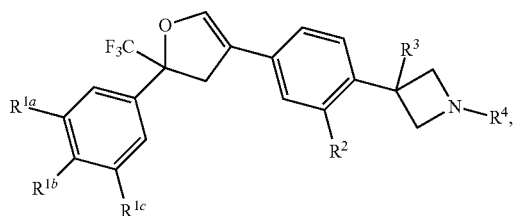
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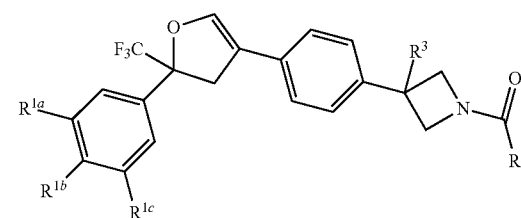
In yet another aspect of the invention are compounds of Formula (2a), (2b), (2c), (2d), (2e), (2f), (3a), (4a), (4b), (5a), (6a), and (6b).



(2a)



(2b)

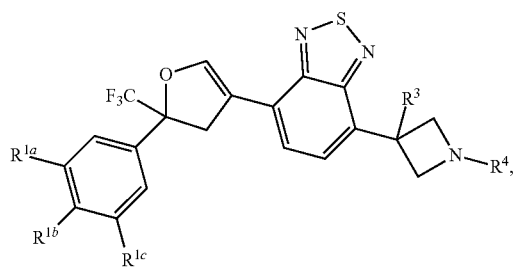
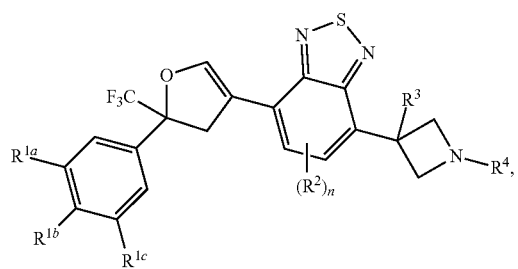
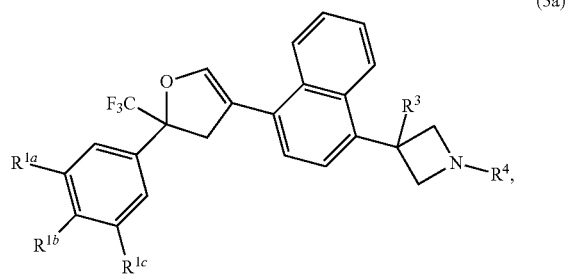
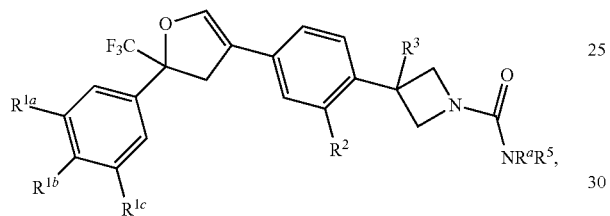
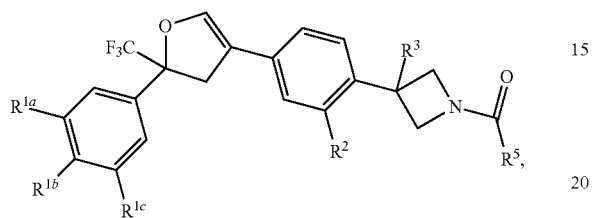
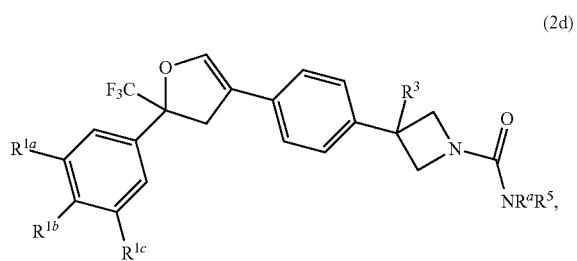


(2c)

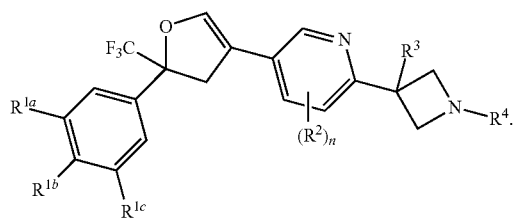
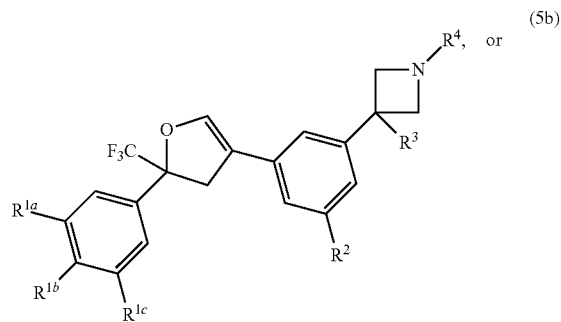
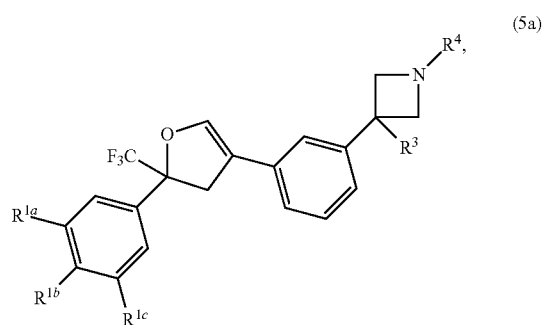
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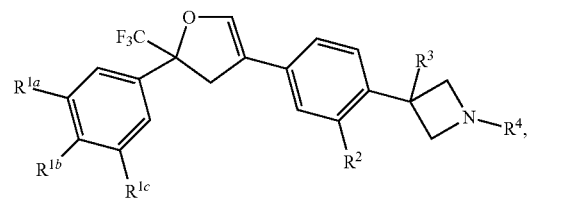
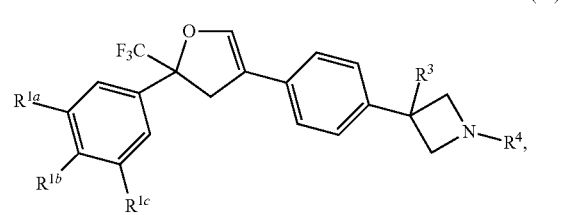
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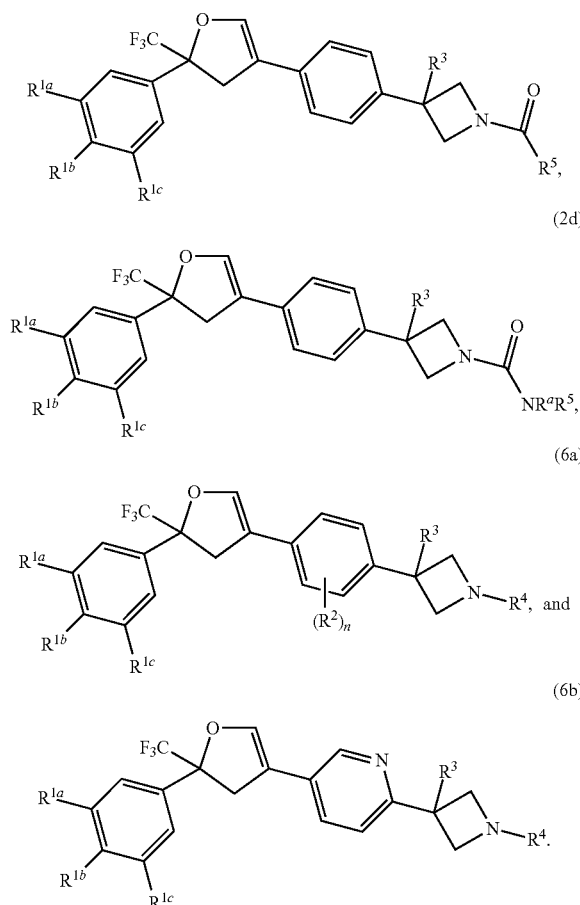


In yet another aspect of the invention are compounds of Formula (2a), (2b), (2c), (2d), (6a), and (6b).

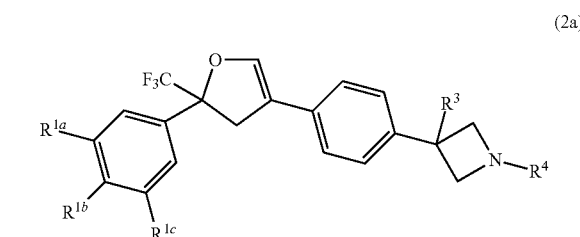


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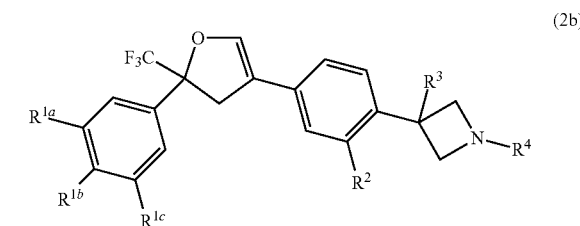
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In yet another aspect of the invention are compounds of Formula (2a).

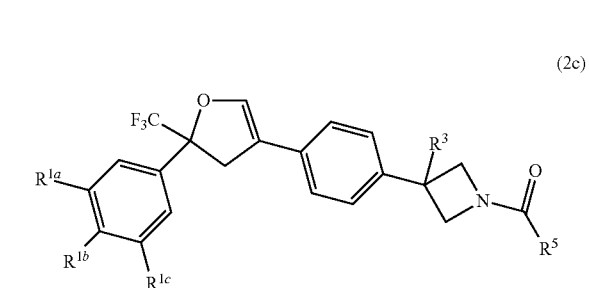


In yet another aspect of the invention are compounds of Formula (2b).



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In yet another aspect of the invention are compounds of Formula (2c).



In yet another aspect of the invention are Formula (2c) compounds selected from 1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;

1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;

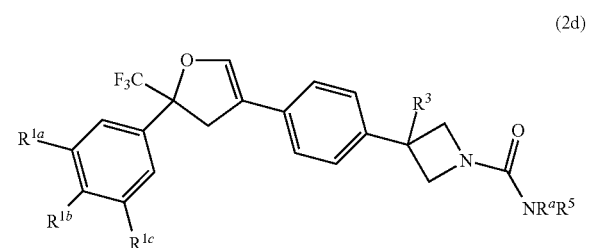
1-(3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone;

1-(3-Fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-di-hydro-furan-3-yl]-phenyl}-azetidin-1-yl)-2-methyl-propan-1-one;

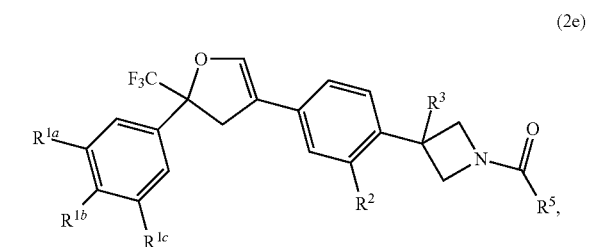
1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone; and

1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methyl-propan-1-one, stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

In yet another aspect of the invention are compounds of Formula (2d).

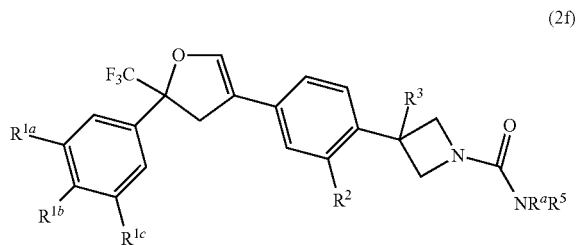


In yet another aspect of the invention are compounds of Formula (2e).

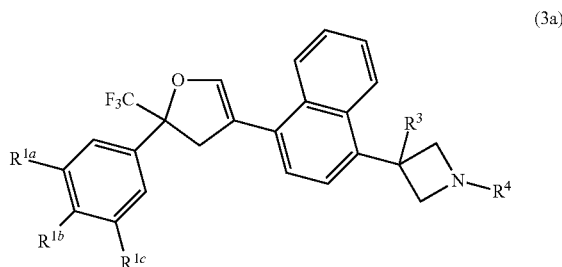


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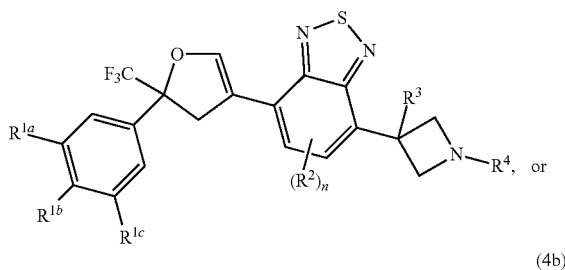
In another aspect of the invention are compounds of Formula (2f).



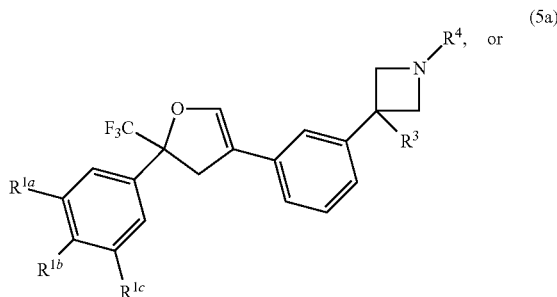
In another aspect of the invention are compounds of Formula (3a).



In another aspect of the invention are compounds of Formula (4a) and (4b).

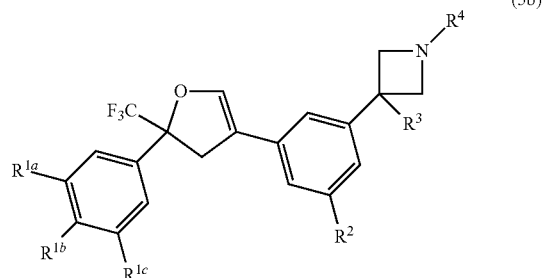


In another aspect of the invention are compounds of Formula (5a) and (5b).

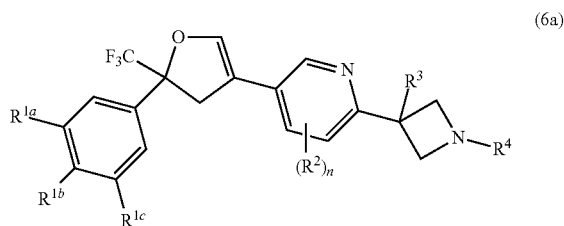


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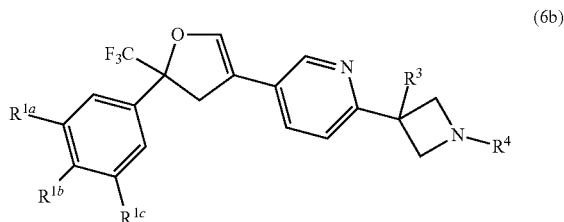
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In yet another aspect of the invention are compounds of Formula (6a).



In yet another aspect of the invention are compounds of Formula (6b).



In another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, halo, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{0-3} alkyl C_{3-6} cycloalkyl, $-S(O)_pR$, and $-SF_5$. In yet another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, halo, hydroxyl, cyano, C_{1-6} haloalkyl, and C_{0-3} alkyl C_{3-6} cycloalkyl. In yet another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, halo, hydroxyl, cyano, and C_{1-6} haloalkyl. In yet another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, fluoro, chloro, bromo, cyano, and C_{1-6} haloalkyl. In yet another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, fluoro, chloro, bromo, and $-CF_3$. In yet another aspect of the invention, each of R^{1a} , R^{1b} and R^{1c} are independently selected from hydrogen, fluoro, chloro, and $-CF_3$.

In yet another aspect of the invention, the integer n of $(R^2)_n$ is 2. When the integer n is 2, then each R^2 may be identical or different from each other. In yet another aspect of the invention, the integer n of $(R^2)_n$ is 1. In yet another aspect of the invention, the integer n of $(R^2)_n$ is 0.

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In yet another aspect of the invention, R^2 is selected from halo, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, hydroxyl, $-C(O)NR^aR^b$, C_2 - C_6 alkenyl, or $-OR$. In yet another aspect of the invention, R^2 is selected from halo, cyano, C_1 - C_6 haloalkyl, hydroxyl, $-C(O)NR^aR^b$, or $-OR$. In yet another aspect of the invention, R^2 is selected from halo, cyano, $-C(O)NR^aR^b$, or hydroxyl. In yet another aspect of the invention, R^2 is selected from cyano or $-C(O)NR^aR^b$, or hydroxyl. In yet another aspect of the invention, R^2 is selected from cyano. In yet another aspect of the invention, R^2 is selected from $-C(O)NR^aR^b$.

In another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, $-SC(O)R$, $-C(O)NR^aR^b$, C_0 - C_3 alkyl NR^aR^4 , $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3 , $-NHR^4$, $-OR$, or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, $-C(O)NR^aR^b$, C_0 - C_3 alkyl NR^aR^4 , $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3 , $-NHR^4$, or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, $-C(O)NR^aR^b$, C_0 - C_3 alkyl NR^aR^4 , $-NR^aNR^bR^4$, $-NHR^4$, N_3 , or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, $-C(O)NR^aR^b$, $-NHR^4$, N_3 , or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, or N_3 .

In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or N_3 . In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, or N_3 . In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, or N_3 . In yet another aspect of the invention, R^3 is hydrogen, fluoro, chloro, bromo, N_3 , hydroxyl, or cyano. In yet another aspect of the invention, R^3 is hydrogen, fluoro, chloro, N_3 , hydroxyl, or cyano. In yet another aspect of the invention, R^3 is hydrogen. In yet another aspect of the invention, R^3 is fluoro. In yet another aspect of the invention, R^3 is chloro. In yet another aspect of the invention, R^3 is hydroxyl. In yet another aspect of the invention, R^3 is cyano. In yet another aspect of the invention, R^3 is N_3 .

In another aspect of the invention, R^4 is C_1 - C_6 alkyl, C_0 - C_6 alkyl C_3 - C_6 cycloalkyl, $-C(O)R^5$, $-C(S)R^5$, $-C(O)NR^aR^5$, $-C(O)C(O)NR^aR^5$, $-S(O)_pR^c$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$, $-C(NR^7)NR^aR^5$, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle; wherein each of R^4 and R^5 C_1 - C_6 alkyl or C_0 - C_6 alkyl C_3 - C_6 cycloalkyl can be optionally and independently substituted as described herein, and wherein each of R^a , R^c , R^4 and R^5 substituents can be optionally and independently substituted as described herein. In yet another aspect of the invention, R^4 is $-C(O)R^5$, $-C(O)NR^aR^5$, $-S(O)_pR^c$, $-C(S)R^5$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$, or $-C(NR^7)NR^aR^5$, and wherein each of R^a , R^c , and R^5 substituents can be optionally and independently substituted as described herein. In yet another aspect of the invention, R^4 is $-C(O)R^5$, or $-C(O)NR^aR^5$, and wherein each of R^a and R^5 substituents can be optionally and independently substituted as described herein.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is hydrogen, C_1 - C_6 alkyl, C_0 - C_6 alkyl C_3 - C_6 cycloalkyl, C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle, wherein said R^5 C_1 - C_6 alkyl or C_0 - C_6 alkyl C_3 - C_6 cycloalkyl can be optionally and indepen-

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dently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, $-S(O)_pR^c$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^c$, $-SCN$, or $-C(O)NR^aR^b$, where said R^5 C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-SH$, $-S(O)_pR$, and C_1 - C_6 haloalkoxy. The R^a and R^c substituents are also optionally substituted with at least one substituent as defined herein.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is hydrogen, C_1 - C_6 alkyl, C_0 - C_6 alkyl C_3 - C_6 cycloalkyl, or C_0 - C_6 alkylheteroaryl, where said C_0 - C_6 alkyl C_3 - C_6 cycloalkyl or C_0 - C_6 alkylheteroaryl moieties are optionally substituted as defined herein. In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$ -cyclopropyl, $-CH_2$ -cyclobutyl, $-CH_2$ -cyclopentyl, $-(CH_2)_2$ -cyclopropyl, $-(CH_2)_2$ -cyclobutyl, $-(CH_2)_2$ -cyclopentyl, pyrazolyl, $-CH_2$ -pyrazolyl, $-(CH_2)_2$ -pyrazolyl, pyridinyl, $-CH_2$ -pyridinyl, $-(CH_2)_2$ -pyridinyl, wherein the alkyl (for example, methyl, ethyl, and propyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, $-CH_2$ -cyclopropyl and $-(CH_2)_2$ -cyclobutyl) can be optionally and independently substituted as defined herein.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$ -cyclopropyl, $-CH_2$ -cyclobutyl, $-CH_2$ -cyclopentyl, $-(CH_2)_2$ -cyclopropyl, $-(CH_2)_2$ -cyclobutyl, $-(CH_2)_2$ -cyclopentyl, pyrazolyl, $-CH_2$ -pyrazolyl, $-(CH_2)_2$ -pyrazolyl, pyridinyl, $-CH_2$ -pyridinyl, $-(CH_2)_2$ -pyridinyl, wherein the alkyl (for example, methyl, ethyl, and propyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, $-CH_2$ -cyclopropyl and $-(CH_2)_2$ -cyclobutyl) can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, methoxy, $-CF_3$, ethoxy, $-S(O)_pR$, $-SCH_3$, $-SCH_2CH_3$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NH(CH_2)_2CH_3$, $-NH$ cyclopropyl, $-NH$ cyclobutyl, $-NHCH_2$ cyclopropyl, $-NHCH_2$ cyclobutyl, $-NR^aC(O)R^b$, or $-C(O)NH_2$.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$ -cyclopropyl, $-CH_2$ -cyclobutyl, $-CH_2$ -cyclopentyl, pyrazolyl, $-CH_2$ -pyrazolyl, pyridinyl, $-CH_2$ -pyridinyl, wherein the alkyl (for example, methyl, ethyl, and isopropyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, $-CH_2$ -cyclopropyl) can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, $-CF_3$, $S(O)_pR$, methoxy, ethoxy, $-SCH_3$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NH$ cyclopropyl, $-NH$ cyclobutyl, $-NHC(O)H$, or $-C(O)NH_2$.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$ -cyclopropyl, $-CH_2$ -cyclobutyl, $-CH_2$ -cyclopentyl, pyrazolyl, $-CH_2$ -pyrazolyl, pyridinyl, $-CH_2$ -pyridinyl, wherein the alkyl (for example, methyl, ethyl, and isopropyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, $-CH_2$ -cyclopropyl) can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, $-CF_3$, methoxy, $-SCH_3$, $S(O)_pR$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NH$ cyclopropyl, $-NHC(O)H$, or $-C(O)NH_2$.

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In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is oxetane, thiatane, azetidine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, $-CH_2$ -oxetane, $-CH_2$ -thiatane, $-CH_2$ -azetidine, or $-CH_2$ -tetrahydrofuran, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is oxetane, thiatane, azetidine, tetrahydrofuran, tetrahydrothiophene, $-CH_2$ -oxetane, $-CH_2$ -thiatane, or $-CH_2$ -azetidine, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is oxetane, thiatane, azetidine, $-CH_2$ -oxetane, $-CH_2$ -thiatane, or $-CH_2$ -azetidine, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is oxetane, thiatane, or azetidine, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is $-CH_2$ -oxetane, $-CH_2$ -thiatane, or $-CH_2$ -azetidine, each of which are optionally substituted as defined herein.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, pyridine, pyridazine, pyrazine, or pyrimidine, each of the which are optionally substituted as defined herein.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_0 - C_6 alkyl/ C_3 - C_6 cycloalkyl, wherein each of C_1 - C_6 alkyl or C_0 - C_6 alkyl/ C_3 - C_6 cycloalkyl is optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, $-S(O)_pR^c$, C_1 - C_6 alkoxy, $-S(O)_pNR^aR^b$, or $-SC(O)R^c$; pyrazole, pyridine, oxazole, pyridazine, triazole, azetidine, thiatane, wherein each heterocycle and heteroaryl moiety are optionally substituted further with at least one substituent selected from fluoro, hydroxyl, methyl, and oxo; where p , R^a , R^b , and R^c are as defined herein.

In yet another aspect of the invention, when R^4 is $-C(O)NR^aR^5$, then R^a is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$ -cyclopropyl, $-CH_2$ -cyclobutyl, $-CH_2$ -cyclopentyl, $-(CH_2)_2$ -cyclopropyl, $-(CH_2)_2$ -cyclobutyl, or $-(CH_2)_2$ -cyclopentyl; wherein the alkyl (for example methyl and propyl), cycloalkyl (for example, cyclopropyl and cyclopentyl), or the alkylcycloalkyl (for example, $-CH_2$ -cyclopropyl, $-CH_2$ -cyclopentyl, and $-(CH_2)_2$ -cyclobutyl) are optionally substituted by cyano or at least one halo substituent; and R^5 is as defined herein.

In yet another aspect of the invention, when R^4 is $-C(O)NR^aR^5$, then R^a is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$ -cyclopropyl, $-CH_2$ -cyclobutyl, $-CH_2$ -cyclopentyl; wherein the alkyl (for example, methyl and propyl), cycloalkyl (for example, cyclopropyl and cyclopentyl), or the alkylcycloalkyl (for example, $-CH_2$ -cyclopropyl and $-CH_2$ -cyclopentyl) are optionally substituted by cyano or at least one halo substituent; and R^5 is as defined herein.

In yet another aspect of the invention, when R^4 is $-C(O)NR^aR^5$, then R^a is hydrogen or methyl and R^5 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, and C_0 - C_6 alkyl/heterocycle, wherein the alkyl and alkylheterocycle moiety are each optionally substituted as described herein.

In yet another aspect of the invention, when R^4 is $-S(O)_pR^c$, the integer p is 2, and R^c is as defined herein, and said R^c substituent is optionally substituted with at least one substituent as defined herein. In yet another aspect of the invention, when R^4 is $-S(O)_pR^c$, the integer p is 2, R^c is C_1 - C_6 alkyl optionally substituted with at least one substituent as defined

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herein. In yet another aspect of the invention, when R^4 is $-S(O)_pR^c$, the integer p is 2, R^c is C_1 - C_6 alkyl optionally substituted with at least one substituent selected from cyano or halo. In yet another aspect of the invention, when R^4 is $-S(O)_pR^c$, the integer p is 2, and R^c is C_1 - C_6 alkyl. In yet another aspect of the invention, when R^4 is $-S(O)_pR^c$, the integer p is 2, and R^c is methyl, ethyl, propyl, or isopropyl. In yet another aspect of the invention, when R^4 is $-S(O)_pR^c$, the integer p is 2, and R^c is methyl or ethyl.

In yet another aspect of the invention, R^6 is cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or $-C(O)NH_2$. In yet another aspect of the invention, R^6 is cyano, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl. In yet another aspect of the invention, R^6 is cyano, methyl, ethyl, or C_1 - C_6 haloalkyl. In yet another aspect of the invention, R^6 is cyano, methyl, or C_1 - C_6 haloalkyl. In yet another aspect of the invention, R^6 is cyano or C_1 - C_6 haloalkyl. In yet another aspect of the invention, R^6 is C_1 - C_6 haloalkyl. In yet another aspect of the invention, R^6 is $-CF_3$, $-CHF_2$, $-CH_2F$, and $-CF_2Cl$. In yet another aspect of the invention, R^6 is $-CF_3$, $-CHF_2$, and $-CH_2F$. In yet another aspect of the invention, R^6 is $-CF_3$.

In yet another aspect of the invention, R is methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, or cyclopentyl. In yet another aspect of the invention, R is methyl, ethyl, isopropyl, cyclopropyl, or cyclobutyl.

In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, isopropyl, or isobutyl, each alkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, or isopropyl, each alkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl, or ethyl, each alkyl is optionally substituted as defined herein.

In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$ -cyclopropyl, or $-CH_2$ -cyclobutyl, each alkyl, cycloalkyl, and alkylcycloalkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, $-CH_2$ -cyclopropyl, or $-CH_2$ -cyclobutyl, each alkyl, cycloalkyl, and alkylcycloalkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, $-CH_2$ -cyclopropyl, or $-CH_2$ -cyclobutyl, each alkyl, cycloalkyl, and alkylcycloalkyl moiety is optionally substituted as defined herein.

In another aspect of the invention, R^b is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, or C_0 - C_3 alkylheteroaryl. In yet another aspect of the invention, R^b is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, or C_0 - C_3 alkylheteroaryl. In yet another aspect of the invention, R^b is hydrogen, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl. In yet another aspect of the invention, R^b is hydrogen, methyl, ethyl, isopropyl, propyl, isobutyl, cyclopropyl, or cyclobutyl.

In yet another aspect of the invention is a composition that comprises a) a Formula (1) compound, stereoisomers thereof, or a veterinarily or pharmaceutically acceptable salt thereof, and (b) a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier. The variables R^{1a} , R^{1b} , R^{1c} , R^2 , R^3 , R^4 , R^5 , and n are as defined herein. Preferably, the composition comprises a therapeutically effective amount of a Formula (1) compound, stereoisomer thereof, or veterinarily or pharmaceutically acceptable salt thereof, and a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier. The composition may comprise at least one additional veterinary agent. Preferred additional veterinary agents include

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endoparasiticides, endectocides, ectoparasiticides, insecticides, and anthelmintics, and are described herein.

The composition may comprise at least one additional veterinary agent. Preferred additional veterinary agents include endoparasiticides, endectocides, ectoparasiticides, insecticides, and anthelmintics, and are described herein. In one aspect of the invention, the additional veterinary agent is selected from amitraz, amino acetonitriles, anthelmintics (e.g., albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, oxfendazole, oxfendazole, oxibendazole, paraherquamide, parbendazole, piperazines, praziquantel, thiabendazole, tetramisole, triclabendazole, levamisole, pyrantel pamoate, oxantel, morantel, and the like), avermectins (e.g., abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, and the like), milbemycin, milbemycin oxime, demiditraz, diethylcarbamazine, fipronil, hydroprene, kinoprene, methoprene, metaflumizone, niclosamide, permethrin, pyrethrins, pyriproxyfen, and spinosad. In another aspect of the invention, the additional agent is selected from an amino acetonitrile, albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, oxfendazole, oxibendazole, paraherquamide, parbendazole, praziquantel, thiabendazole, tetramisole, triclabendazole, levamisole, pyrantel pamoate, oxantel, morantel, abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, milbemycin, milbemycin oxime, demiditraz, diethylcarbamazine, fipronil, hydroprene, kinoprene, methoprene, metaflumizone, niclosamide, pyriproxyfen, and spinosad. In yet another aspect of the invention, the additional agent is selected from an amino acetonitrile, paraherquamide, praziquantel, abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, milbemycin, and milbemycin oxime. In yet another aspect of the invention, the additional agent is selected from abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, milbemycin, and milbemycin oxime. In yet another aspect of the invention, the additional agent is selected from moxidectin, selamectin, and milbemycin oxime. In yet another aspect of the invention, the additional agent is selected from moxidectin and milbemycin oxime.

In yet another aspect of the invention is the use of a Formula (1) compound for the manufacture of a medicament.

In yet another aspect of the invention is a method for treating a parasitic infection or infestation in an animal that includes the step of administering to said animal, in need of such treatment, a therapeutically effective amount of a compound of the present invention, stereoisomer thereof, or veterinarily acceptable salt thereof. In one aspect, the animal is a mammal, specifically a companion animal (for example, dog, cat, or horse) or livestock (for example, sheep, goat, cattle, and pig). In another aspect, the animal is a bird, specifically, fowl (for example, chicken, turkey, duck, and geese). In another aspect, the animal is a fish. The compounds of the present invention, and compositions thereof, can be administered to the animal orally or topically. The compounds of the present invention, and compositions thereof, can also be administered to the animal by intramuscular-, intraperitoneal-, or subcutaneous-injection. Preferably, the compounds of the present invention, and compositions thereof, can be administered to the animal orally or topically.

In yet another aspect of the invention is a method for treating a parasitic infection or infestation in an animal that includes the step of administering to said animal, in need of

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such treatment, a therapeutically effective amount of a compound of the present invention, stereoisomer thereof, or veterinarily acceptable salt thereof, in combination with at least one additional veterinary agent. In one aspect, the animal is a mammal, specifically a companion animal (for example, dog, cat, or horse) or livestock (for example, sheep, goat, cattle, and pig). In another aspect, the animal is a bird, specifically, fowl (for example, chicken, turkey, duck, and geese). In another aspect, the animal is a fish. The compounds of the present invention, and compositions thereof, can be administered to the animal orally or topically. The compounds of the present invention, and compositions thereof, can also be administered to the animal by intramuscular-, intraperitoneal-, or subcutaneous-injection. Preferably, the compounds of the present invention, and compositions thereof, can be administered to the animal orally or topically. Equally preferred, the compounds of the present invention can be administered by injection.

Compounds of the present invention alone, or in combination with an additional veterinary agent(s) may be administered as (a) a single veterinary composition which comprises a compound of the present invention, stereoisomer thereof, veterinarily acceptable salt thereof, and optionally, at least one additional veterinary agent as described herein and a veterinarily acceptable excipient, diluent, or carrier; or (b) two separate veterinary compositions comprising (i) a first composition comprising a compound of the present invention, stereoisomer thereof, veterinarily acceptable salt thereof, and a veterinarily acceptable excipient, diluent, or carrier, and (ii) a second composition comprising at least one additional veterinary agent, as described herein and a veterinarily acceptable excipient, diluent, or carrier. The veterinary compositions may be administered simultaneously or sequentially and in any order.

All of the recited WO patent publications herein are incorporated by reference.

DEFINITIONS

For purposes of the present invention, as described and claimed herein, the following terms and phrases are defined as follows:

“Additional veterinary agent(s)” as used herein, unless otherwise indicated, refers to other veterinary or pharmaceutical compounds or products that provide a therapeutically effective amount of said agents that are useful for the treatment of a parasitic infection in an animal, as described herein.

“Alkoxy”, as used herein, unless otherwise indicated, refers to an oxygen moiety having a further alkyl substituent. The alkyl portion (i.e., alkyl moiety) of an alkoxy group has the same definition as below. Non-limiting examples include: $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, and the like.

“Alkyl”, as used herein, unless otherwise indicated, refers to saturated monovalent hydrocarbon alkane radicals of the general formula $\text{C}_n\text{H}_{2n+1}$. The alkane radical may be straight or branched and may be unsubstituted or substituted. For example, the term “(C₁-C₆)alkyl” refers to a monovalent, straight or branched aliphatic group containing 1 to 6 carbon atoms. Non-exclusive examples of (C₁-C₆) alkyl groups include, but are not limited to methyl, ethyl, propyl, isopropyl, sec-butyl, t-butyl, n-propyl, n-butyl, i-butyl, s-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, 2-methylpentyl, hexyl, and the like. The alkyl moiety may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Alkyl groups are optionally substituted as described herein. Further when used in compound words such as alkylphenyl, said alkyl

moiety has the same meaning as herein defined and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Non-limiting examples of the compound word, alkylphenyl include: C_1 alkylphenyl is $-CH_2$ phenyl, C_2 alkylphenyl is $-CH_2CH_2$ phenyl, C_6 phenyl is phenyl, and the like.

"Alkenyl" as used herein, unless otherwise indicated, refers to a straight or branched aliphatic hydrocarbon chain having 2- to 6-carbon atoms and containing at least one carbon-carbon double bond (for example $-C=C-$, or $-C=CH_2$). Non-exclusive examples of alkenyl include: ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-pentenyl, and the like.

"Alkynyl" as used herein, unless otherwise indicated, refers to straight or branched aliphatic hydrocarbon chain having 2- to 6-carbon atoms and containing at least one carbon-carbon triple bond (for example, $-C\equiv C-$ or $-C\equiv CH$). Non-exclusive examples of alkynyl include: ethynyl, 2-propynyl, 1-methyl-2-propynyl, 2-butylnyl, 3-butylnyl, 2-methyl-3-butylnyl, and the like.

"Animal(s)" as used herein, unless otherwise indicated, refers to an individual animal that is a mammal, bird, or fish. Specifically, mammal refers to a vertebrate animal that is human and non-human, which are members of the taxonomic class Mammalia. Non-exclusive examples of non-human mammals include companion animals and livestock. Non-exclusive examples of a companion animal include: dog, cat, llama, and horse. Preferred companion animals are dog, cat, and horse. More preferred is dog. Non-exclusive examples of livestock include: swine, camel, rabbits, goat, sheep, deer, elk, bovine (cattle), and bison. Preferred livestock is cattle and swine. Specifically, bird refers to a vertebrate animal of the taxonomic class Aves. Birds are feathered, winged, bipedal, endothermic, and egg-laying. Non-exclusive examples of bird include, poultry (e.g., chicken, turkey, duck, and geese), all of which are also referred to herein as fowl. Specifically, fish refers to the taxonomic class Chondrichthyes (cartilaginous fishes, e.g., sharks and rays) and Osteichthyes (bony fishes) which live in water, have gills or mucus-covered skin for respiration, fins, and may have scales. Non-exclusive examples of fish include shark, salmon, trout, whitefish, catfish, tilapia, sea bass, tuna, halibut, turbot, flounder, sole, striped bass, eel, yellowtail, grouper, and the like.

"Carbocyclic", as used herein, unless otherwise indicated, refers to a partially saturated or saturated 5- to 7-membered ring containing only carbon atoms and can be monocyclic or part of a fused ring or spiro ring moiety. Examples of carbocyclic rings include cyclopentane, cyclohexane, and cycloheptane. The carbocyclic ring is optionally substituted as described herein.

"Chiral", as used herein, unless otherwise indicated, refers to the structural characteristic of a molecule that makes it impossible to superimpose it on its mirror image, (e.g., "R" and "S" enantiomers). The term is also depicted as an asterisk (i.e., *) in the Examples and preparations and refers to a chiral center which includes both the S and R enantiomers.

"Compounds of the present invention", as used herein, unless otherwise indicated, refers to compounds of Formula (1) compounds, and stereoisomers thereof.

"Cycloalkyl", as used herein, unless otherwise indicated, includes fully saturated or partially saturated carbocyclic alkyl moieties. Non-limiting examples of partially saturated cycloalkyls include: cyclopropene, cyclobutene, cycloheptene, cyclooctene, cyclohepta-1,3-diene, and the like. Preferred cycloalkyls are 3- to 6-membered saturated monocyclic rings including cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The cycloalkyl group may be attached to the

chemical moiety by any one of the carbon atoms within the carbocyclic ring. Cycloalkyl groups are optionally substituted with at least one substituent. Further when used in compound words such as alkylcycloalkyl, said alkyl and cycloalkyl moiety has the same meaning as herein defined and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Examples of C_0 - C_6 alkyl C_3 - C_6 cycloalkyl include, methylcyclopropane (C_1 alkyl C_3 cycloalkyl or $-CH_3$ cyclopropane), ethylcyclopropane (C_2 alkyl C_3 cycloalkyl or $-CH_2CH_3$ cyclopropane), methylcyclobutane (C_1 alkyl C_4 cycloalkyl or $-CH_3$ cyclobutane), ethylcyclobutane (C_2 alkyl C_4 cycloalkyl or $-CH_2CH_3$ cyclobutane), methylcyclohexane (C_1 alkyl C_6 cycloalkyl or $-CH_3$ cyclohexane), and the like. C_0 alkyl C_3 - C_6 cycloalkyl is C_3 - C_6 cycloalkyl. Cycloalkyl moieties are optionally substituted as described herein.

"Halogen" or "halo", as used herein, unless otherwise indicated, refers to fluorine, chlorine, bromine and iodine. Further, when used in compound words such as "haloalkyl", "haloalkoxy", "haloalkenyl", or "haloalkynyl", said alkyl, alkoxy, alkenyl, and alkynyl may be partially or fully substituted with halogen atoms which may be the same or different and said alkyl, alkoxy, alkenyl, and alkynyl moiety has the same meaning as above and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Examples of "haloalkyl" include F_3C- , $ClCH_2-$, CF_3CH_2- and CF_3CCl_2- , and the like. The term "haloalkoxy" is defined analogously to the term "haloalkyl". Examples of "haloalkoxy" include CF_3O- , CCl_3CH_2O- , $HCF_2CH_2CH_2O-$ and CF_3CH_2O- , and the like. The term "haloalkenyl" is defined analogously to the term "haloalkyl" except that the aliphatic chain contains at least one carbon-carbon double bond. Examples of "haloalkenyl" include $CF_3C=C-$, $CCl_3C=C-$, $HCF_2C=C-$ and $CF_3C=CC-$, and the like. The term "haloalkynyl" is defined analogously to the term "haloalkyl" except that the aliphatic chain contains at least one carbon-carbon triple bond. Examples of "haloalkynyl" include $CF_3C\equiv C-$, $CCl_3C\equiv C-$, $HCF_2C\equiv C-$ and $CF_3C\equiv CC-$, and the like.

"Heteroaryl" or "Het", as used herein, unless otherwise indicated, refers to a 5- to 6-membered aromatic monocyclic ring or an 8- to 10-membered fused aromatic ring where said monocyclic- and fused-ring moiety contains one or more heteroatoms each independently selected from N, O, or S, preferably from one to four heteroatoms. Non-exclusive examples of monocyclic heteroaryls include pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like. Non-exclusive examples of fused heteroaryls include: benzofuranyl, benzothiophenyl, indolyl, benzimidazolyl, indazolyl, benzotriazolyl, thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, benzo[1,2,5]thiadiazole, and the like. The heteroaryl group may be attached to the chemical moiety by any one of the carbon atoms or nitrogen heteroatoms within the monocyclic or fused ring. Further when used in compound words such as alkylheteroaryl, said alkyl and heteroaryl moiety have the same meaning as herein defined and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. For example, C_0 alkylheteroaryl is heteroaryl, C_1 alkylheteroaryl is $-CH_2$ heteroaryl, C_0 alkylheteroaryl is $-CH_2CH_2$ heteroaryl, and the like. Heteroaryls are optionally substituted as described herein.

"Heterocycle", as used herein, unless otherwise indicated, refers to a partially saturated or saturated 3- to 7-membered monocyclic ring containing one or more heteroatoms each

independently selected from N, O, or S, preferably from one to four heteroatoms. The heterocyclic ring can be part of a fused ring or spiro-ring moiety. Non-exclusive examples of heterocycle include oxirane, thiarane, aziridine, oxetane, azetidine, thiatane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydropyran, piperidine, piperazine, tetrahydropyridine, 2H-azirine, 2,3-dihydro-azete, 3,4-dihydro-2H-pyrrole, and the like. The heterocycle group may be attached to the chemical moiety by any one of the carbon atoms or nitrogen heteroatoms within the ring. Further when used in compound words such as alkylheterocycle, said alkyl and heterocycle moiety have the same meaning as herein defined and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. For example, C₀alkylheterocycle is heterocycle, C₁alkylheterocycle is —CH₂heterocycle, C₀alkylheterocycle is —CH₂CH₂heterocycle, and the like. Heterocycles are optionally substituted as described herein.

“Optionally substituted”, is used herein interchangeably with the phrase substituted or unsubstituted. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other. An optionally substituted group also may have no substituents. Therefore, the phrase “optionally substituted with at least one substituent” means that the number of substituents may vary from zero up to a number of available positions for substitution.

“Parasite(s)”, as used herein, unless otherwise indicated, refers to endoparasites and ectoparasites. Endoparasites are parasites that live within the body of its host and include helminths (e.g., trematodes, cestodes, and nematodes) and protozoa. Ectoparasites are organisms of the Arthropoda phylum (e.g., arachnids, insects, and crustaceans (e.g., copepods-sea lice) which feed through or upon the skin of its host. Preferred arachnids are of the order Acarina, e.g., ticks and mites. Preferred insects are midges, fleas, mosquitos, biting flies (stable fly, horn fly, blow fly, horse fly, and the like), bed bugs, and lice. Preferred compounds of the present invention can be used for the treatment of parasites, i.e., treatment of a parasitic infection or infestation.

“Protecting group” or “Pg”, as used herein, unless otherwise indicated, refers to a substituent that is commonly employed to block or protect an amine on the compound thereby protecting its functionality while allowing for the reaction of other functional groups on the compound. Non-exclusive examples of an amine-protecting group include: acyl groups (e.g., formyl, acetyl, chloroacetyl, trichloroacetyl, o-nitrophenylacetyl, o-nitrophenoxycarbonyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl, and the like), acyloxy groups (e.g., 1-tert-butyloxycarbonyl (Boc), methoxycarbonyl, 9-fluorenyl-methoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, 1,1-dimethyl-propynyloxycarbonyl, benzyloxy-carbonyl, p-nitrobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, and the like), diphenylmethane, and benzylcarbamates.

“Therapeutically effective amount”, as used herein, unless otherwise indicated, refers to an amount of the compounds of the present invention that (i) treat the particular parasitic infection or infestation, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular parasitic infection or infestation, or (iii) prevents or delays the onset of one or more symptoms of the particular parasitic infection or infestation described herein.

“Treatment”, “treating”, and the like, as used herein, unless otherwise indicated, refers to reversing, alleviating, or inhibiting the parasitic infection, infestation, or condition. As used herein, these terms also encompass, depending on the condition of the animal, preventing the onset of a disorder or condition, or of symptoms associated with a disorder or condition, including reducing the severity of a disorder or condition or symptoms associated therewith prior to affliction with said infection or infestation. Thus, treatment can refer to administration of the compounds of the present invention to an animal that is not at the time of administration afflicted with the infection or infestation. Treating also encompasses preventing the recurrence of an infection or infestation or of symptoms associated therewith as well as references to “control” (e.g., kill, repel, expel, incapacitate, deter, eliminate, alleviate, minimize, and eradicate).

“Veterinary acceptable” as used herein, unless otherwise indicated, indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, composition, and/or the animal being treated therewith. The term “pharmaceutically” acceptable has the same meaning as that recited for “veterinarily” acceptable.

DETAILED DESCRIPTION

The present invention provides Formula (1) compounds, stereoisomers thereof, as well as veterinary compositions that are useful as antiparasitic agents for animals, in particular, compounds that act as ectoparasiticides.

Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, “Reagents for Organic Synthesis”, 1; 19, Wiley, New York (1967, 1999 ed.), or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)). For illustrative purposes, the reaction schemes depicted below demonstrate potential routes for synthesizing compounds of the present invention, and key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. A skilled artisan will appreciate that other suitable starting materials, reagents, and synthetic routes may be used to synthesize the compounds of the present invention and a variety of derivatives thereof. Further, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to the skilled artisan.

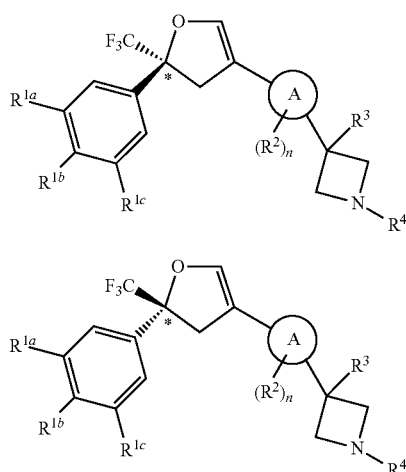
Compounds of the present invention described herein contain at least one asymmetric or chiral center; and, therefore, exist in different stereoisomeric forms. The R and S configurations are based upon knowledge of known chiral inversion/retention chemistry. Unless specified otherwise, it is intended that all stereoisomeric forms of the compounds of the present invention as well as mixtures thereof, including racemic mixtures and diastereomeric mixtures, form part of the present invention.

Enantiomeric mixtures can be separated into their individual enantiomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as chromatography and/or fractional crystallization. A

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more detailed description of techniques that can be used to resolve stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley and Sons, Inc. (1981).

Compounds of this invention can exist as one or more stereoisomers. The various stereoisomers include enantiomers, diastereomers and atropisomers. One skilled in the art will appreciate that one stereoisomer may be more active and/or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to separate, enrich, and/or to selectively prepare said stereoisomers. The compounds of the invention may be present as a mixture of stereoisomers, individual stereo isomers or as an optically active form. For example, two possible enantiomers of Formula 1 are depicted as Formula 1a and Formula 1b involving the spirocyclic isoxazoline chiral center identified with an asterisk (*). Molecular depictions drawn herein follow standard conventions for depicting stereochemistry.



For illustrative purposes, the reaction schemes depicted below demonstrate potential routes for synthesizing key intermediates and compounds of the present invention. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other suitable starting materials, reagents, and synthetic routes may be used to synthesize the intermediates and compounds of the present invention and a variety of derivatives thereof. Further, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry. Schemes 1-10 outline the general procedures useful for the preparation and isolation of compounds of the present invention. It is to be understood, however, that the invention, as fully described herein and as recited in the claims, is not intended to be limited by the details of the following schemes or modes of preparation.

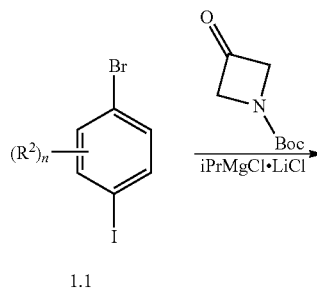
In the preparation of compounds of the present invention, protection of remote functionality of intermediates from undesired reactions can be accomplished with a protecting group. The term "protecting group" or "Pg" refers to a sub-

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stituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an amine-protecting group is a substituent attached to an amine that blocks or protects the amine-functionality of the compound or intermediate. Suitable amine protecting groups include: 1-tert-butyloxycarbonyl (Boc), acyl groups including: formyl, acetyl, chloroacetyl, trichloro-acetyl, o-nitrophenylacetyl, o-nitro-phenoxyacetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl, and the like; and acyloxy groups including: methoxycarbonyl, 9-fluorenyl-methoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, 1,1-dimethyl-propyloxycarbonyl, benzyloxy-carbonyl, p-nitrobenzyloxy-carbonyl, 2,4-dichlorobenzyloxycarbonyl, and the like. Similarly, diphenylmethane and benzylcarbamates can be used as amine protecting groups. Suitable protecting groups and their respective uses are readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991.

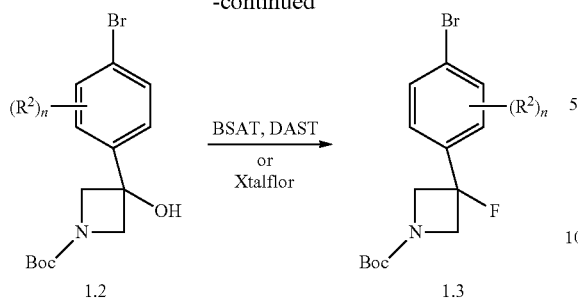
In the Schemes and Examples below, the following catalysts/reactants and miscellaneous abbreviations include: N,N-dimethyl formamide (DMF); dimethyl acetamide (DMA); tetrahydrofuran (THF); trifluoroacetic acid (TFA); dimethyl ether (DME); triphenylphosphine palladium (Pd (PPh₃)₄); N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU); isopropylmagnesium chloride (iPrMgCl); t-butyloxycarbonyl (BOC); n-butyllithium (n-BuLi); triethylamine (Et₃N); dichloromethane (CH₂Cl₂); Bis(2-methoxyethylaminosulfur trifluoride (BSAT); diethylaminosulfur trifluoride (DAST); dichloroethane (DCE); palladium(II)[1,3-bis(diphenylphosphino)propane] (PD dppp); carbonyldiimidazole (CDI); tetrabutylammonium fluoride (TBAF); 4-dimethylaminopyridine (DMAP); Bis(1,5-cyclooctadienediiridium(1) dichloride ([Ir(COD)]₂); 4,4-di-tert-butyl bipyridine (dtbpy); bis(pinacolato)diboron (B₂pin₂); trimethylsilyldiazomethane (TMSCHN₂); and isopropylamine (iPrNH₂); triethyl amine (TEA); dichloromethane (DCM); methanol (MeOH); potassium hexamethyldisilazane (KHMDs); dimethylsulfoxide (DMSO); N,N-diisopropylethylamine (DIPEA); and propane phosphonic acid anhydride (T₃P).

Scheme 1



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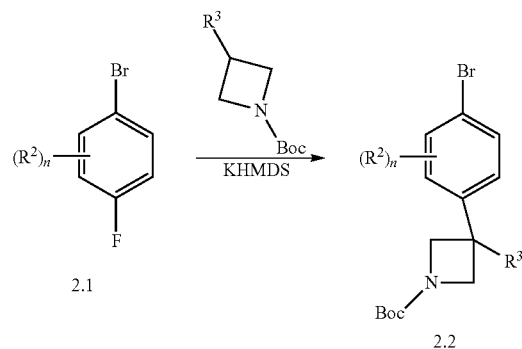
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R^2 and n are as defined herein.

Compounds of Formula 2.2 (below) can be prepared using methods illustrated in Scheme 1. Selective Grignard metallation of the bromiodobenzene 1.1 and addition to a protected azetidinone provides the phenylazetidine derivatives 1.2. The hydroxyl functionality can be further manipulated such as by treatment with a fluorinating agent (BAST, DAST or Xtalflor) to provide additional analogs of the phenylazetidines 1.3.

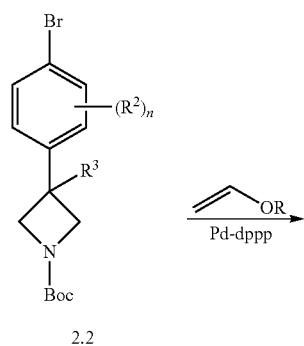
Scheme 2



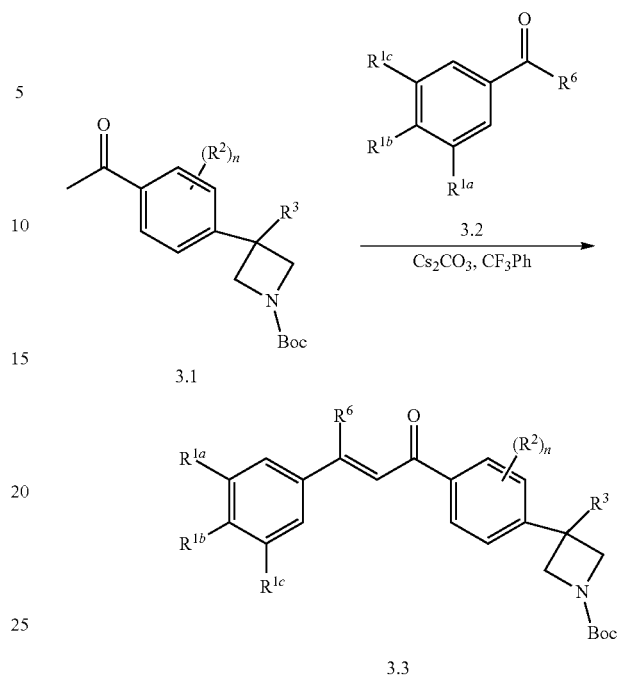
R^2 , R^3 , and n are as defined herein.

Alternatively, compounds of Formula 2.2 can be prepared using methods illustrated in Scheme 2. When R^3 is an electron withdrawing group (CN, CO_2R , SO_2R , etc), deprotonation of the azetidine ring can be accomplished by treatment with KHMDS. This metallated species can then undergo S_NAr displacement reaction of the fluorine of the bromofluorobenzene 2.1 to provide substituted azetidine analogs of Formula 2.2. Other substituted phenylazetidines can be purchased from commercial sources or prepared using procedures analogous to those found in literature (see for example: WO2012017359 or Justus Liebigs Annalen der Chemie (1961), 647 83-91).

Scheme 3

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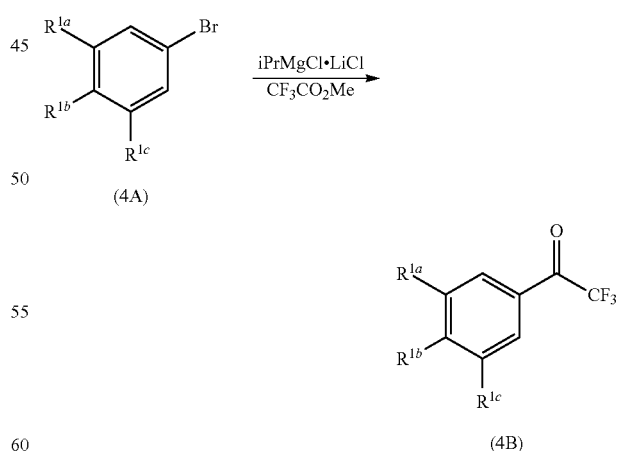
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R , R^{1a} , R^{1b} , R^{1c} , R^2 , R^3 , R^6 , and n are as defined herein.

Compounds of Formula 3.3 can be prepared using methods illustrated by Scheme 3. Palladium catalyzed condensation of the bromophenylazetidine 2.2 with a vinyl ether provides the acetophenone 3.1 which can undergo condensation with a substituted phenylketone derivative 3.2 in the presence of a base such as cesium carbonate to give the enone 3.3. The phenylketone derivative can be prepared by reacting bromobenzene with an ethyl ester in the presence of a Grignard reagent.

Scheme 4

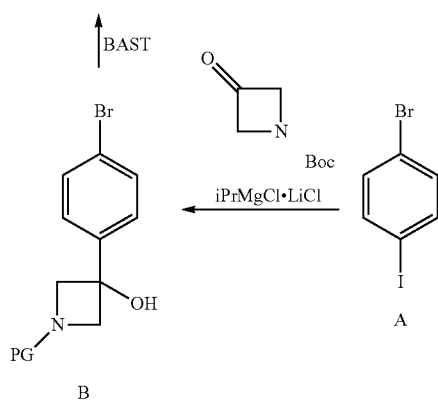
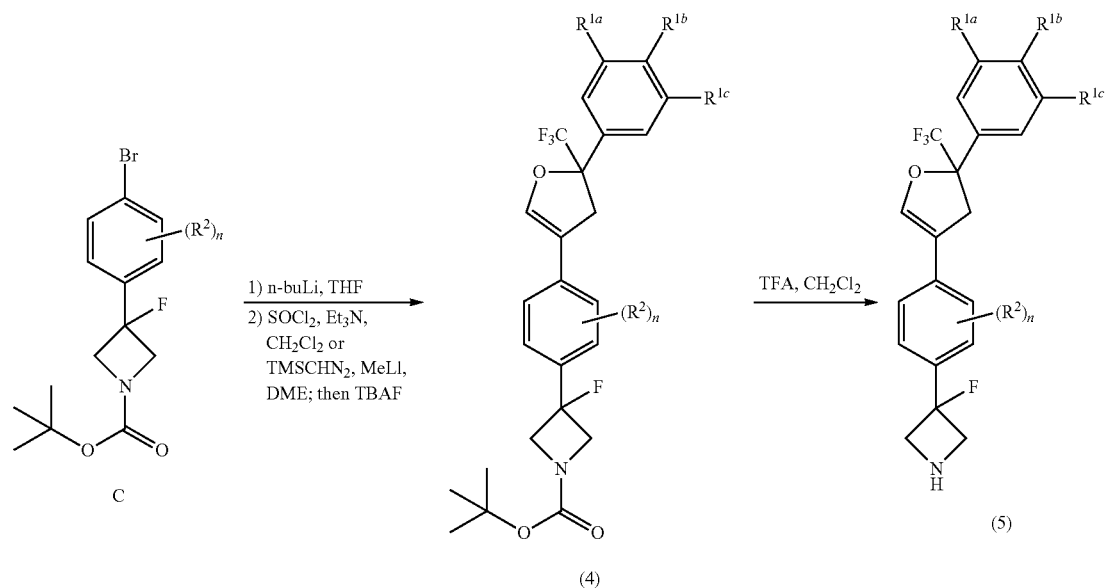
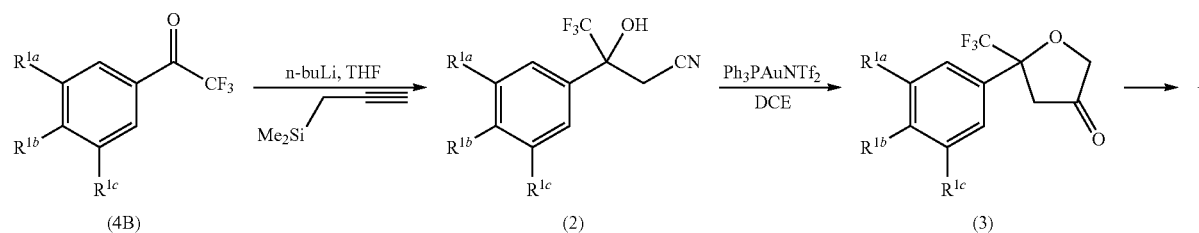


The requisite trifluorophenylethanone derivatives 4B can be prepared according to Scheme 4. Metallation of the aryl bromide 4A under modified Grignard conditions and addition to ethyl 2,2,2-trifluoroacetate provides the substituted trifluorophenyl-ethanones 4B.

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Scheme 5a

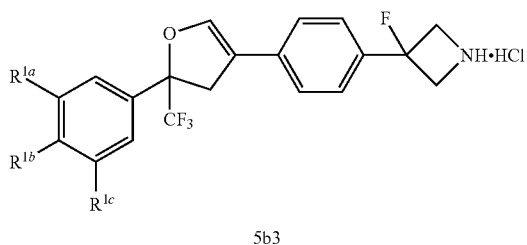
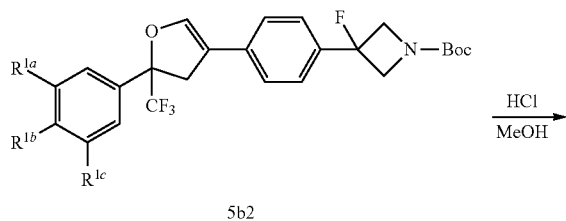
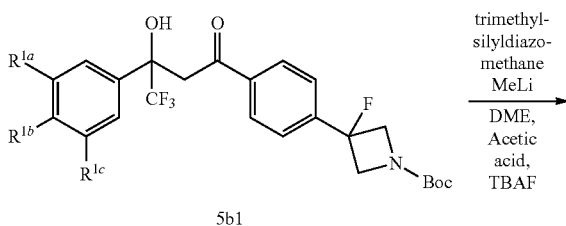
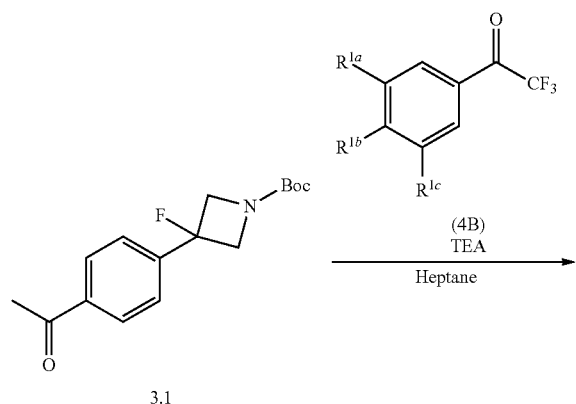


Scheme 5a describes the preparation of the 2,3-dihydrofuran compounds from the bromophenyl azetidine C and the dihydrofuranone 3. The dihydrofuranone 3 is prepared by a two step procedure, initially involving the addition of trimethylsilylpropyne to the aryl olefin 4B in the presence of a strong base and a subsequent hydrative cyclization of the resulting alcohol 2 in the presence of a suitable Lewis acid as described in *J. Am. Chem. Soc.*, 2010, 132 (10), pp 3258-3259. Halogen-metal exchange mediated addition of the bro-

mophenyl azetidine C to the dihydrofuranone 3 affords the 2,3-dihydrofuran 4. Removal of the Boc protecting group can be achieved by treatment with trifluoroacetic acid to provide azetidine 5. The bromophenyl azetidine C can be prepared by metallation of bromiodobenzene A under modified Grignard conditions, condensation with a protected azetidinone to form the hydroxyazetidinone B and fluorination of B with a fluorinating agent such as BAST, DAST or Xtalfluor.

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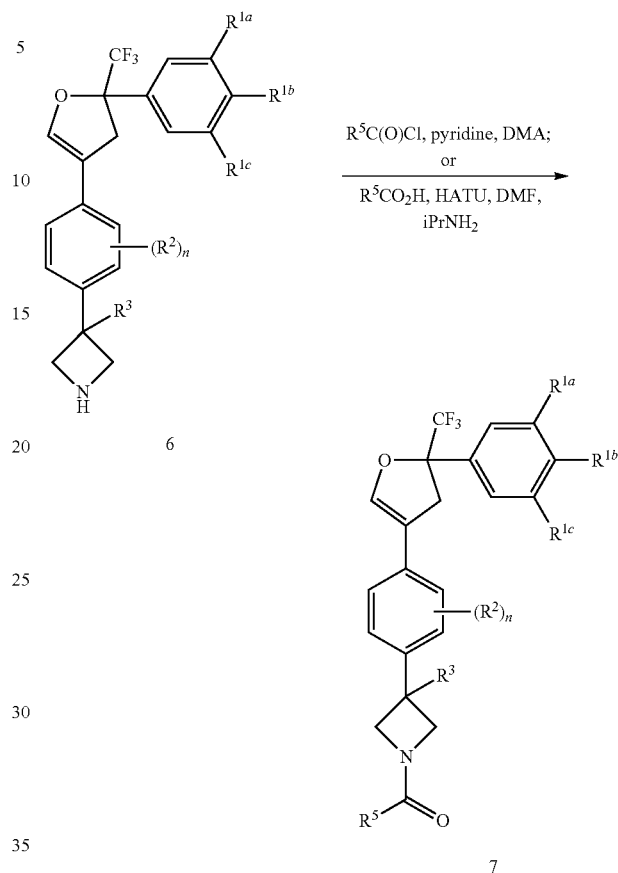
Scheme 5b



Condensation of the acetophenone 3.1 with a substituted trifluoroacetophenone (4B) in the presence of a base such as triethylamine provides the β -hydroxyketone 5b1. Condensation of 5b1 with trimethylsilyldiazomethane and subsequent cyclization provides the dihydrofuran 5b2. Removal of the Boc protecting group can be accomplished with acidic conditions such as HCl in methanol or trifluoroacetic acid to provide the azetidine 5b3.

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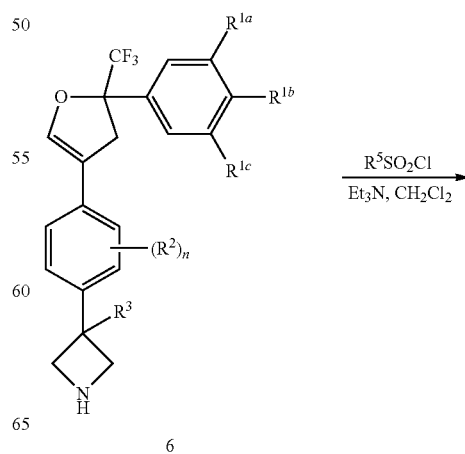
Scheme 6



R^{1a}, R^{1b}, R^{1c}, R², R³, R⁵, and n are as defined herein.

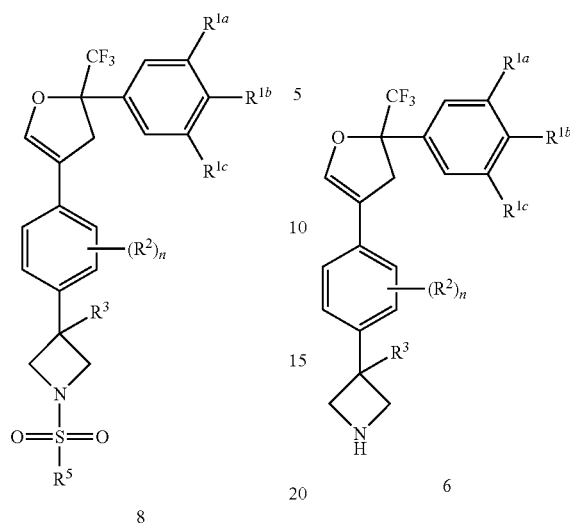
Amide analogs of the azetidine ring can be prepared as shown in Scheme 6. Acylation of the azetidine 6 with an acid chloride in pyridine/DMA or by a condensation with a carboxylic acid utilizing a condensing agent such as HATU or HOBT to afford compound 7.

Scheme 7



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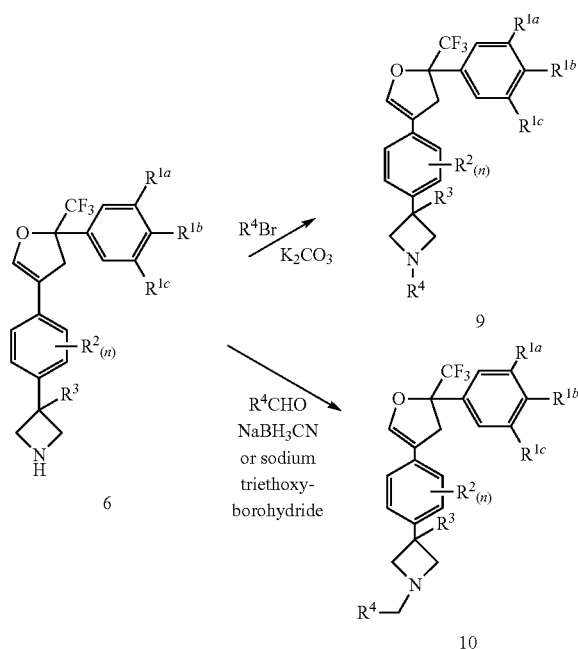
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R^{1a} , R^{1b} , R^{1c} , R^2 , R^3 , R^5 , and n are as defined herein.

Sulfonamide analogs of the azetidine ring can be prepared as shown in Scheme 7. Reaction of azetidine 6 with sulfonyl chlorides in the presence of triethylamine can give the desired sulfonamides 8.

Scheme 8

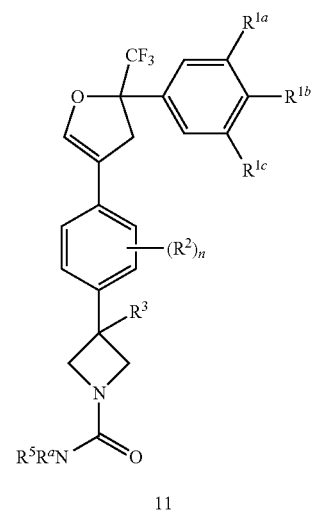
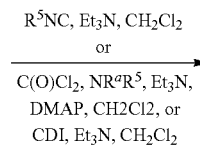


R^{1a} , R^{1b} , R^{1c} , R^2 , R^3 , R^4 , and n are as defined herein.

Compounds in which R^4 is alkyl or substituted alkyl can be prepared from the azetidine 6 by standard alkylation chemistry or by reductive amination with the corresponding aldehydes as shown in Scheme 8.

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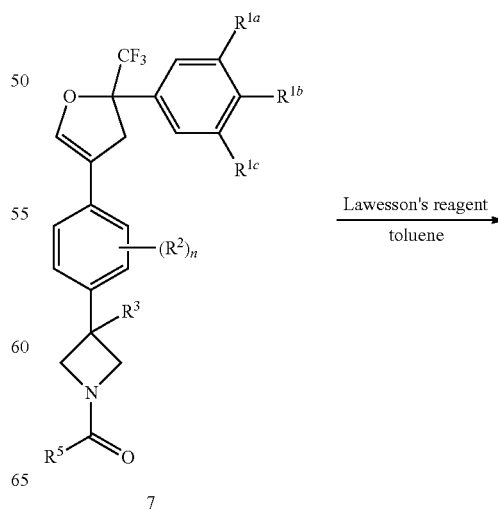
Scheme 9



R^{1a} , R^{1b} , R^{1c} , R^2 , R^3 , R^a , R^5 , and n are as defined herein.

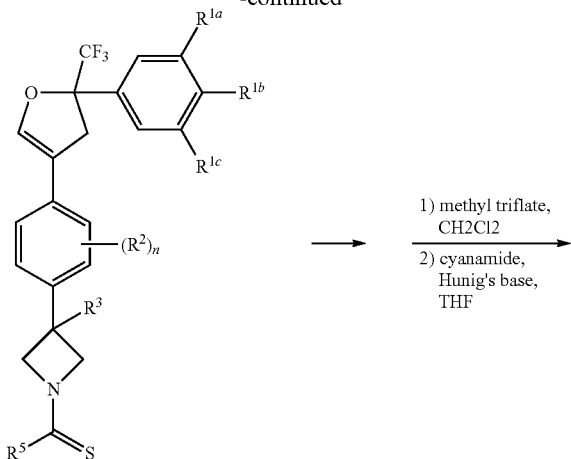
Urea analogs can be prepared as shown in Scheme 9. Reaction of the azetidine 6 with an isocyanate or preformed carbamoyl chloride in the presence of a tertiary amine base provides the ureas.

Scheme 10

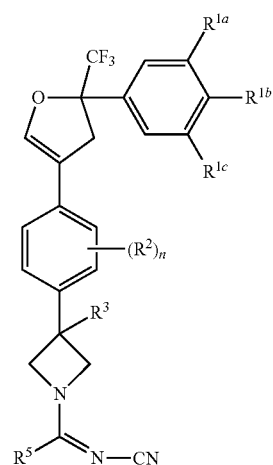


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Thioamide 12 can be prepared by treatment of amide 7 with Lawesson's reagent in refluxing toluene. Methyl triflate can be added to thioamide 12 in a solvent such as CH_2Cl_2 to form a thioimide intermediate as a solution. Cyanamide and Hunig's base in THF can be subsequently added directly to the thioimide solution to afford cyanamide 13.

One skilled in the art will recognize that, in some cases, after the introduction of a given reagent as it is depicted in the schemes, it may be necessary to perform additional routine synthetic steps not described in detail to complete the synthesis of Formula (1) compounds.

The present invention includes all veterinarily acceptable isotopically-labelled Formula (1) compounds wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the present invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , and sulphur, such as ^{35}S .

The skilled person will appreciate that the compounds of the present invention could be made by methods other than those herein described as incorporated herein by reference, by adaptation of the methods herein described and/or adaptation

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of methods known in the art, for example the art described herein, or using standard textbooks such as "Comprehensive Organic Transformations—A Guide to Functional Group Transformations", RC Larock, Wiley-VCH (1999 or later editions).

The Formula (1) compounds are useful as ectoparasitic and endoparasitic agents, therefore, another embodiment of the present invention is a veterinary or pharmaceutical composition comprising a therapeutically effective amount of a Formula (1) compound, stereoisomer thereof, and a veterinarily or pharmaceutically acceptable excipient, diluent or carrier. The compounds of the present invention (including the compositions and processes used therein) may also be used in the manufacture of a medicament for the therapeutic applications described herein.

A typical formulation is prepared by mixing a Formula (1) compound with a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe to be administered to an animal. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or veterinary composition thereof) or aid in the manufacturing of the veterinary or pharmaceutical product (i.e., medicament). The formulations can be prepared using conventional dissolution and mixing procedures. Such compositions and methods for their preparation may be found, for example, in 'Remington's Veterinary Sciences', 19th Edition (Mack Publishing Company, 1995; and "Veterinary Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., 1980 (ISBN 0-8247-6918-X). For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more other excipients. The compounds of the present invention are typically formulated into veterinary or pharmaceutical dosage forms to provide an easily controllable dosage form for administration. Compounds of the present invention can also be admixed with animal feed.

The compounds may be administered alone or in a formulation appropriate to the specific use envisaged, the particular species of host animal being treated and the parasite involved. Generally, they will be administered as a formulation in association with one or more veterinarily or pharmaceutically acceptable salts, excipients, diluents, or carriers. The term "excipient", "diluent" or "carrier" is used herein to describe any ingredient other than the Formula (1) compounds or any additional antiparasitic agent. The choice of excipient, diluent, or carrier will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient, carrier, or diluent on solubility and stability, nature of the dosage form, and animal specie.

The methods by which the compounds of the present invention may be administered include oral, topical, and injectable (subcutaneous, intraperitoneal, and intramuscular)

administration. The preferred method of administration of the Formula (1) compounds is in an oral solid dosage form or oral liquid dosage form. Equally preferred is topical administration.

The Formula (1) compounds can be administered orally by capsule, bolus, tablet, powders, lozenges, chews, multi and nanoparticulates, gels, solid solution, films, sprays, liquid form, or admixed with food. Oral administration is the preferred method of administration and as such it is desirable to develop active Formula (1) compounds that are particularly suited to such formulations. Such formulations may be employed as fillers in soft or hard capsules, tablets, or chews, and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, N-methylpyrrolidone, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid forms include suspensions, solutions, syrups, drenches and elixirs. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet. Oral drenches are commonly prepared by dissolving or suspending the active ingredient in a suitable medium. Feed admixtures can be prepared for livestock and fish. Oral formulations can comprise from about 0.5 mg/kg to 50 mg/kg of a Formula (1) compound, and preferably about 1 mg/kg to 30 mg/kg of a Formula (1) compound. Depending upon the host specie treated and the parasite being treated, dose adjustments can be made.

The compounds may be administered topically to the skin or mucosa, that is dermally or transdermally. This is a preferred method of administration and as such it is desirable to develop active Formula (1) compounds that are particularly suited to such formulations, for example liquid forms. Typical formulations for this purpose include pour-on, spot-on, multi-spot-on, stripe-on, comb-on, roll-on, dip, spray, mousse, shampoo, powder formulation, gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and micro emulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, N-methyl formamide, glycol monomethyl ethers, polyethylene glycol, propylene glycol, and the like. Penetration enhancers may be incorporated—see, for example, *J Pharm Sci*, 88 (10), 955-958 by Finnin and Morgan (October 1999). Pour-on or spot-on formulations may be prepared by dissolving the active ingredients in an acceptable liquid carrier vehicle such as butyl digol, liquid paraffin or a non-volatile ester, optionally with the addition of a volatile component such as propan-2-ol or a glycol ether. Alternatively, pour-on, spot-on or spray formulations can be prepared by encapsulation, to leave a residue of active agent on the surface of the animal, this effect may ensure that the Formula (1) compounds have increased persistence of action and are more durable, for example they may be more water fast. Topical formulations of the combination contemplated herein can comprise from about 0.5 mg/kg to 50 mg/kg of a Formula (1) compound, and preferably about 1 mg/kg to 10 mg/kg of a Formula (1) compound. The compositions suitable for spot-on application according to the invention can be prepared by conventional mixing means. The volume of the applied composition can be from about 0.5 mL/kg to 5 mL/kg and preferably from about 1 mL/kg to 3 mL/kg. Similarly, dose can be adjusted.

The compounds of the present invention can also be administered topically via a support matrix for example, a synthetic or natural resin, plastic, cloth, leather, or other such polymeric system in the shape of a collar or ear tag. Said collar or ear tag may be coated, impregnated, layered, by any means so as to provide a veterinarily or pharmaceutically acceptable amount

of a compound of the present invention alone, or with a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier, and optionally an additional veterinary agent, or veterinarily or pharmaceutically acceptable salt thereof.

Agents may be added to the formulations of the present invention to improve the persistence of such formulations on the surface of the animal to which they are applied, for example to improve their persistence on the coat of the animal. It is particularly preferred to include such agents in a formulation which is to be applied as a pour-on or spot-on formulation. Examples of such agents include acrylic copolymers and in particular fluorinated acrylic copolymers. A particular suitable reagent is the trademark reagent "Foraperle" (Redline Products Inc, Texas, USA). Certain topical formulations may include unpalatable additives to minimize oral exposure.

Injectable formulations may be prepared in the form of a sterile solution, which may contain other substances, for example enough salts or glucose to make the solution isotonic with blood. Acceptable liquid carriers include vegetable oils such as sesame oil, glycerides such as triacetin, esters such as benzyl benzoate, isopropyl myristate and fatty acid derivatives of propylene glycol, as well as organic solvents such as pyrrolidin-2-one and glycerol formal. The formulations are prepared by dissolving or suspending compounds of the present invention alone or with an additional veterinary agent in the liquid carrier such that the final formulation contains from about 0.01 to 50% by weight of the active ingredients, preferably from about 0.01% to about 10% by weight of the active ingredients.

Suitable devices for injection include needle (including micro needle) injectors, needle-free injectors and infusion techniques. Subcutaneous formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dry powder form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of subcutaneous formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard veterinary techniques well known to those skilled in the art. The solubility of compounds of Formula (1) used in the preparation of subcutaneous solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Such formulations are prepared in a conventional manner in accordance with standard medicinal or veterinary practice. Further, these formulations will vary with regard to the weight of active compound contained therein, depending on the species of host animal to be treated, the severity and type of infection or infestation, and the body weight of the animal.

For fish, compounds of the present invention can be formulated for oral administration by way of feed admixture. For example, the compounds of the present invention can be formulated in a food product (e.g., pellets) that can be easily dispersed to fish as a feeding agent. Further, a compound of the present invention can be administered topically by immersing the fish into an aqueous environment containing at least one of the compounds of the present invention. For example, fish may be transferred into a tank for treatment or caused to pass from one holding zone into another. The compounds of the present invention may also be administered directly to the water containing the fish. The compound of the present invention can be in any dispersible formulation such that upon introduction to water the compound dissolves into the solution. Alternatively, the compounds of the present

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invention can be administered by injection. Preferable injection routes for treatment of fish are intraperitoneal or intramuscular. The injectable formulations include any liquid suspension, such as oils, aqueous solutions, or oil and water emulsions. The compounds of the present invention can also be co-administered with additional agents, antigens, adjuvants, carriers, diluents or nutrients.

The Formula (1) compounds are also active against all or individual developmental stages of animal pests showing normal sensitivity, as well as those showing resistance to widely used parasiticides.

As described herein, compounds of the present invention may be administered alone or in combination with at least one additional veterinary agent including insecticides, acaricides, anthelmintics, fungicides, nematocides, antiprotozoals, bactericides, and growth regulators to form a multi-component agent giving an even broader spectrum of veterinary utility. Thus, the present invention also pertains to a composition comprising an effective amount of a Formula (1) compound, a stereoisomer thereof, and an effective amount of at least one additional veterinary agent and can further comprise one or more of a veterinary or pharmaceutically acceptable excipient, diluent, or carrier.

The following list of additional veterinary agents together with which the compounds of the present invention can be used is intended to illustrate the possible combinations, but not to impose any limitation. Non-limiting examples of additional veterinary agents include: amitraz, arylpyrazoles as recited in publications WO1998/24767 and WO2005/060749, amino acetonitriles, anthelmintics (e.g., albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, octadepsipeptides, oxfendazole, oxiabendazole, paraherquamide (2-desoxoparaherquamide, derquantel), parbendazole, piperazines, praziquantel, thiabendazole, tetramisole, triclabendazole, levamisole, pyrantel pamoate, oxantel, morantel, and the like), indoxacarb and derivatives thereof, avermectins (e.g., abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, and the like), milbemycin, milbemycin oxime, DEET, demiditraz, diethylcarbamazine, fipronil, insect growth regulators (e.g., hydroxyurea, kinoprene, methoprene, pyriproxyfen, and the like), metaflumizone, niclosamide, permethrin, pyrethrins, spinosad, and formamidines (e.g., demiditraz, amitraz, and the like). In certain instances, combinations of a Formula (1) compound with an additional veterinary agent(s) can result in a greater-than-additive effect. Reducing the quantity of active ingredients released in the environment while ensuring effective pest control is always desirable.

It may be desirable to administer a compound of the present invention, stereoisomers thereof, alone or in a composition comprising a veterinary acceptable excipient, diluent, or carrier, for example, for the purpose of treating a particular parasitic infection or infestation or condition associated therewith. It is within the scope of the present invention that two or more veterinary compositions, at least one of which contains a Formula (1) compound in accordance with the invention, and the other, an additional veterinary agent, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

The compounds of the present invention (including the compositions and processes used therein) may also be used in the manufacture of a medicament for the therapeutic applications described herein.

The compounds of the present invention, stereoisomers thereof, and compositions comprising a therapeutically effective amount of a Formula (1) compound and a veterinary acceptable excipient, diluent, or carrier are useful as parasiti-

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cides (endo- and ecto-parasites) for the control and treatment of infections or infestations manifested by said parasite in an animal. The compounds of the present invention have utility as an ectoparasiticide, in particular, as an acaricide and insecticide. They may, in particular, be used in the fields of veterinary medicine, livestock husbandry, fish farming, and the maintenance of public health: against acarids and insects which are parasitic upon vertebrates, particularly warm-blooded vertebrates, including companion animals, livestock, and birds. The compounds of the present invention are also parasiticides for cold-blooded fish. Some non-limiting examples of acaride and insect parasites include: ticks (e.g., *Ixodes* spp., *Rhipicephalus* spp., *Boophilus* spp., *Amblyomma* spp., *Hyalomma* spp., *Haemaphysalis* spp., *Dermacentor* spp., *Ornithodoros* spp., and the like); mites (e.g., *Dermanyssus* spp., *Sarcoptes* spp., *Psoroptes* spp., *Chorioptes* spp., *Demodex* spp., and the like); chewing and sucking lice (e.g., *Damalinia* spp., *Linognathus* spp., and the like); fleas (e.g., *Siphonaptera* spp., *Ctenocephalides* spp., and the like); biting flies and midges (e.g., *Tabanidae* spp., *Haematobia* spp., *Stomoxys* spp., *Dermatobia* spp., *Simuliidae* spp., *Ceratopogonidae* spp., *Psychodidae* spp., and the like), and bed bugs (e.g., *Cimicidae* spp., particularly, *Cimex lectularius*). In another example, ectoparasites of the crustacean order copepod, more particularly of the genera *Lepeophtheirus* (especially the salmon louse, *Lepeophtheirus salmonis*) and/or Caligus (e.g., *C. elongates*, *C. rogercreysii*, *C. teres*, *C. flexispina*, and the like), particularly sea lice, can be treated with a compound of the present invention. The compounds of the invention can also be used for the treatment of endoparasites, for example, heartworms, roundworms, hookworms, whipworms, and tapeworms.

The compounds of the present invention and compositions comprising compounds of the present invention in conjunction with at least one other veterinary agent are of particular value in the control of ectoparasites, endoparasites, and insects which are injurious to, or spread or act as vectors of diseases in animals. The ectoparasites, insects, and endoparasites which can be treated with a combination of a Formula (1) compound and an additional veterinary agent include those as herein before described and including helminthes of the phylum platyhelminthes (e.g., trematodes, eucestoda, and cestoda), and nemathelminthes (e.g., nematodes).

Any of the compounds of the present invention, or a suitable combination of a compound of the present invention and optionally, with at least one additional veterinary agent may be administered directly to the animal and/or indirectly by applying it to the local environment in which the animal dwells. Direct administration includes contacting the skin, fur, or feathers of a subject animal or bird with the compound (s), or by feeding or injecting the compounds into the animal or bird.

The Formula (1) compounds, stereoisomers thereof, and combinations with at least one additional veterinary agent, as described herein, are of value for the treatment and control of the various lifecycle stages of insects and parasites including egg, nymph, larvae, juvenile and adult stages.

The present invention also relates to a method of administering a compound of the present invention alone or in combination with at least one additional veterinary agent, and optionally a veterinary or pharmaceutically acceptable excipient, diluent, or carrier, to animals in good health comprising the application to said animal to reduce or eliminate the potential for human parasitic infection or infestation from parasites carried by the animal and to improve the environment in which the animal and human inhabit.

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The reactions set forth below were done generally under a positive pressure of argon or nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed using glass-backed silica gel 60 F 254 precoated plates and eluted with appropriate solvent ratios (v/v). Reactions were assayed by TLC or LCMS and terminated as judged by the consumption of starting material. Visualization of the TLC plates was done with UV light (254 nm wavelength) or with an appropriate TLC visualizing solvent and activated with heat. Flash column chromatography (Still et al., *J. Org. Chem.* 43, 2923, (1978) was performed using silica gel (RediSep Rf) or various MPLC systems, such as Biotage or ISCO purification system.

Conventional methods and/or techniques of separation and purification known to one of ordinary skill in the art can be used to isolate the compounds of the present invention, as well as the various intermediates related thereto. Such techniques will be well-known to one of ordinary skill in the art and may include, for example, all types of chromatography (high pressure liquid chromatography (HPLC), column chromatography using common adsorbents such as silica gel, and thin-layer chromatography (TLC), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

The compound structures in the examples below were confirmed by one or more of the following methods: proton magnetic resonance spectroscopy, and mass spectroscopy. Proton magnetic resonance (^1H NMR) spectra were determined using a Bruker spectrometer operating at a field strength of 400 megahertz (MHz). Chemical shifts are reported in parts per million (PPM, δ) downfield from an internal tetramethylsilane standard. Mass spectra (MS) data were obtained using Agilent mass spectrometer with atmospheric pressure chemical ionization. Method: Acquity HPLC with chromatography performed on a Waters BEH C18 column (2.1x50 mm, 1.7 μm) at 50° C. The mobile phase was a binary gradient of acetonitrile (containing 0.1% trifluoroacetic acid) and water (5-100%).

Embodiments of the present invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

Examples

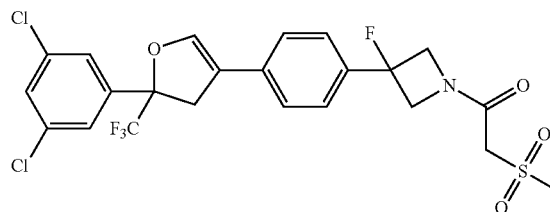
One skilled in the art will also recognize that Formula (1) compounds and the intermediates described herein can be subjected to various electrophilic, nucleophilic, radical, organometallic, oxidation, and reduction reactions to add substituents or modify existing substituents.

The following examples can be prepared according to the schemes presented herein. It is to be understood, however, that the invention, as fully described herein and as recited in the claims, is not intended to be limited by the details of the following schemes or modes of preparation.

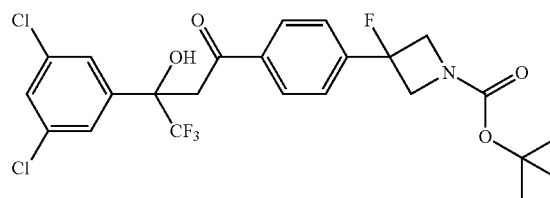
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Example 1

1-(3-{4-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone

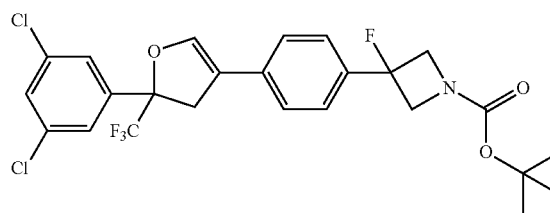


Preparation 1 for Example 1, Intermediate 1, 3-{4-[3-(3,5-dichloro-phenyl)-4,4,4-trifluoro-3-hydroxybutyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester



In a clean and dry seal tube, to a stirred solution of 3-(4-acetyl-phenyl)-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester (4 g, 13.652 mmol, 1eq.) in heptane (40 mL) was added 1-(3,5-dichlorophenyl)-2,2,2-trifluoro-ethanone (6.60 gm, 27.304 mmol, 2eq.) followed by addition of triethyl amine (TEA, 3.80 ml, 27.304 mmol, 2eq.) at room temperature. Resulting reaction mixture was heated at 60° C. for 16 hours. After maximum consumption of starting material, reaction mixture was cooled to room temperature, solid precipitated out. Solid was filtered over Buchner funnel and washed with heptane (2x30 mL) and n-Pentane (70 mL) and dried under reduced pressure to get product as white solid. Yield: ~5.0 g (68.31%). ^1H NMR (400 MHz, CDCl_3) δ : 1.47 (s, 9H), 3.68 (d, $J=17.36$ Hz, 1H), 3.85 (d, $J=17.44$ Hz, 1H), 4.17-4.24 (m, 2H), 4.39-4.47 (m, 2H), 5.69 (s, 1H), 7.33-7.35 (m, 1H), 7.48 (d, $J=1.16$ Hz, 2H), 7.62 (d, $J=8.44$ Hz, 2H), 7.98 (d, $J=8.28$ Hz, 2H). LC-MS (m/z): =534.0 (M-H).

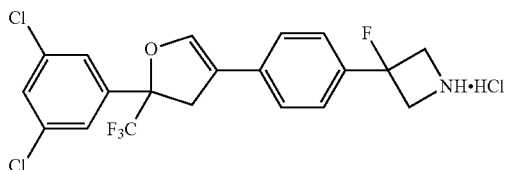
Preparation 2 for Example 1, Intermediate 2, 3-{4-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester



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To a stirred solution of trimethylsilyldiazomethane (2M in diethyl ether, 18.64 mL, 37.289 mmol) in 1,2-dimethoxyethane (DME, 100 mL) was added methyl lithium (1.6M in diethyl ether, 23.32 mL, 37.289 mmol) at -78°C . over period of 10 minutes and stirred reaction mixture for 30 minutes at -78°C . Pre-dissolved 3-{4-[3-(3,5-dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester (Example 1, Intermediate 1) (5 g, 9.322 mmol, 1 eq.) in DME (50 mL) was added at -78°C . in drop wise manner over period of 10 minutes. Resulting reaction mixture was stirred for 1 hour at same temperature and then at room temperature for 2 hours. Acetic acid (1.60 mL, 27.967 mmol, 3 eq.) was added at room temperature over period of 5 minutes followed by addition of TBAF (27.92 mL, 27.967 mmol, 3 eq.) at room temperature over period of 10 minutes. After consumption of starting material, reaction mixture was quenched with water (150 mL) and extracted with ethyl acetate (5x150 mL). Combined organic layer was dried over sodium sulphate and concentrated in vacuo to get orange semisolid (6.1 g, crude). Crude was purified by column chromatography using 100-200 mesh silica gel. Desired compound was eluted in 10% ethyl acetate in hexane to afford off white semisolid (1.6 g, Impure). The product was again purified by trituration using DCM: pentane (1:5, 2x20 mL) to afford product as off white solid (0.45 g, 9.18%). Yield: -0.45 g (9.18%). ^1H NMR (400 MHz, CDCl_3) δ : 1.46 (s, 9H), 3.20 (d, $J=17.24$ Hz, 1H), 3.30 (d, $J=17.24$ Hz, 1H), 4.14-4.21 (m, 2H), 4.33-4.41 (m, 2H), 7.32-7.38 (m, 4H), 7.40 (t, $J=1.78$ Hz, 1H), 7.52 (d, $J=1.36$ Hz, 2H). LC-MS (m/z): =529.9 (M-H).

Preparation 3 for Example 1, Intermediate 1, 3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidine hydrochloride

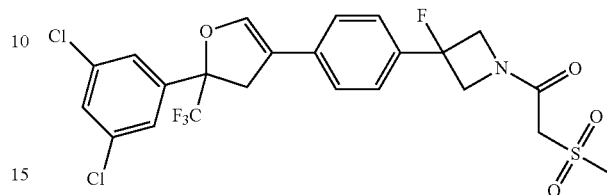


To a stirred solution of 3-{4-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester (Example 1, Intermediate 2) (0.45 g, 0.845 mmol) in MeOH (10 mL) was purged HCl gas for 1 hour at room temperature. After consumption of starting material, reaction mixture concentrated in vacuo to get pale yellow semisolid (0.49 g, crude), which was triturated with n-pentane (2x5 mL) to get off product as white solid. Yield: 0.36 g, 98.53%. ^1H NMR (400 MHz, DMSO- d_6) δ : 3.20 (d, $J=17.16$ Hz, 1H), 3.64 (d, $J=17.16$ Hz, 1H), 4.30-4.54 (m, 4H), 7.29 (d, $J=7.96$ Hz, 2H), 7.48 (s, 1H), 7.52 (d, $J=8$ Hz, 2H), 7.69-7.71 (m, 3H), 9.36 (bs, 2H).

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Example 1

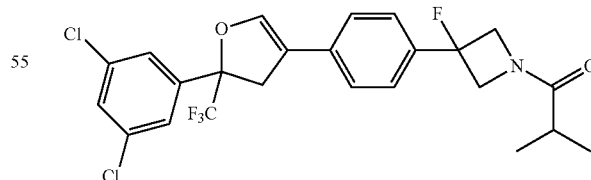
1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone



To a stirred solution of 3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidine hydrochloride (Example 1, Intermediate 3) (0.25 g, 0.535 mmol) in THF (5 mL) was added DIPEA (0.933 mL, 5.35 mmol) at room temperature and stirred for 10 minutes at room temperature. Methane sulfonyl acetic acid (0.147 g, 1.07 mmol), T_3P (50% solution in ethyl acetate, 1.6 mL, 2.675 mmol) were added at room temperature. Resulting reaction mixture was stirred for 16 hours at room temperature under nitrogen atmosphere. After complete consumption of starting material, reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (5x25 mL). Combined organic layer was washed with saturated solution of NaHCO_3 (2x100 mL), dried over sodium sulphate and concentrated in vacuo to get pale yellow oil (0.32 g, crude). Crude was purified by column chromatography using 100-200 mesh silica gel. Desired product gets eluted in 0.6% MeOH in DCM to afford white semisolid (0.160 g), which was triturated with DCM: n-pentane (1:10; 2x5 mL) to afford product as off white solid. Yield: 0.145 g (49.15%). ^1H NMR (400 MHz, DMSO- d_6) δ : 3.11 (s, 3H), 3.20 (d, $J=17.16$ Hz, 1H), 3.65 (d, $J=17.12$ Hz, 1H), 4.24 (s, 2H), 4.34 (d, $J=21.6$ Hz, 2H), 4.70 (d, $J=21.52$ Hz, 2H), 7.27 (d, $J=7.96$ Hz, 2H), 7.47 (d, $J=9.36$ Hz, 2H), 7.73 (d, $J=3.92$ Hz, 3H). LC-MS (m/z): =550.1 (M-H). HPLC purity: 98.75%.

Example 2

1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one



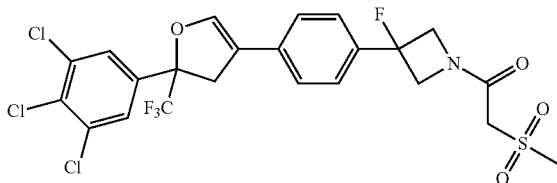
This compound was similarly prepared to that of Example 1, except that isobutyric acid was used in place of methane sulfonyl acetic acid. Yield: 70 mg (65.21%). ^1H NMR (400 MHz, DMSO- d_6) δ : 0.98-1.13 (m, 6H), 2.51-2.55 (m, 1H), 3.20 (d, $J=17.16$ Hz, 1H), 3.65 (d, $J=17.16$ Hz, 1H), 4.23 (d, $J=21.92$ Hz, 2H), 4.60 (d, $J=21.76$ Hz, 2H), 7.26 (d, $J=8.04$

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Hz, 2H), 7.45-7.48 (m, 3H), 7.70-7.71 (m, 3H). LC-MS (m/z): =502.0 (M+H). HPLC purity: 98.70%.

Example 3

1-(3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone



Preparation 1 for Example 3, Intermediate 1, 3-{4-[3-(3,4,5-trichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester, was prepared similarly to Example 1, Intermediate 1, except that 1-(3,4,5-trichlorophenyl)-2,2,2-trifluoro-ethanone was used in place of 1-(3,5-dichlorophenyl)-2,2,2-trifluoro-ethanone. Yield: 8.2 g (93.5%). ¹H NMR (400 MHz, CDCl₃) δ: 1.47 (s, 9H), 3.68 (d, J=17.36 Hz, 1H), 3.84 (d, J=17.44 Hz, 1H), 4.17-4.24 (m, 2H), 4.39-4.47 (m, 2H), 5.70 (s, 1H), 7.61-7.63 (m, 4H), 7.98 (d, J=8.28 Hz, 2H). LC-MS (m/z): =568.0 (M+H).

Preparation 2 for Example 3, Intermediate 2, 3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester, was prepared similarly to Example 1, Intermediate 2, except that 3-{4-[3-(3,4,5-trichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester was used in place of 3-{4-[3-(3,5-dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester. Yield: 0.995 g (13.72%). ¹H NMR (400 MHz, CDCl₃) δ: 1.46 (s, 9H), 3.21 (d, J=17.24 Hz, 1H), 3.31 (d, J=17.8 Hz, 2H), 4.15 (d, J=10.28 Hz, 1H), 4.20 (d, J=10.28 Hz, 1H), 4.35 (d, J=10.2 Hz, 1H), 4.40 (d, J=10.24 Hz, 1H), 7.33-7.37 (m, 4H), 7.65 (s, 2H). LC-MS (m/z): =563.8 (M+H).

Preparation 3 for Example 3, Intermediate 3, 3-fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-azetidine hydrochloride, was prepared similarly to Example 1, Intermediate 3, except that 3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester was used in place of 3-{4-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester. Yield: 0.580 g (Crude, used as such in next step.) ¹H NMR (400 MHz, DMSO-d₆) δ: 3.22 (d, J=17.16 Hz, 1H), 3.68 (d, J=17.16 Hz, 1H), 4.39-4.53 (m, 4H), 7.30 (d, J=8.2 Hz, 2H), 7.54 (d, J=8.16 Hz, 2H), 7.60 (s, 1H), 7.93 (s, 2H), 9.33 (bs, 1H), 9.76 (bs, 1H). LC-MS (m/z): =465.8 (M+H).

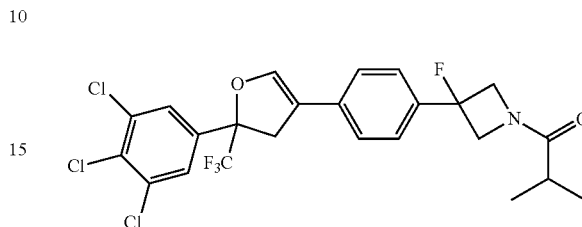
Example 3 was prepared similarly to that of Example 1, except that Example 3, Intermediate 3 was reacted with methane sulfonyl acetic acid. Yield: 0.170 g (29.74%). ¹H NMR (400 MHz, DMSO-d₆) δ: 3.11 (s, 3H), 3.22 (d, J=17.24 Hz, 1H), 3.70 (d, J=17.16 Hz, 1H), 4.24 (s, 2H), 4.34 (d, J=21.64 Hz, 2H), 4.70 (d, J=21.6 Hz, 2H), 7.28 (d, J=8.12 Hz, 2H),

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7.47 (d, J=8.24 Hz, 2H), 7.58 (s, 1H), 7.92 (s, 2H). LC-MS (m/z): =583.8 (M+H). HPLC purity: 99.64%.

Example 4

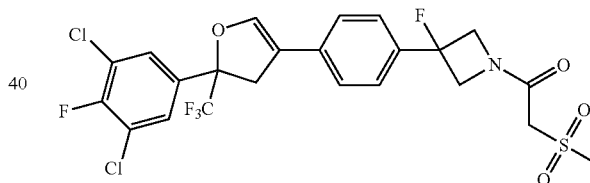
1-(3-fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-azetidin-1-yl)-2-methyl-propan-1-one



This compound was prepared similarly to Example 3, except that isobutyric acid was used in place of methane sulfonyl acetic acid. Yield: 0.115 g (26.71%). ¹H NMR (400 MHz, DMSO-d₆) δ: 0.97-1.01 (m, 6H), 2.52-2.55 (m, 1H), 3.19 (d, J=17.24 Hz, 1H), 3.69 (d, J=17.16 Hz, 1H), 4.24 (d, J=22.08 Hz, 2H), 4.60 (d, J=21.88 Hz, 2H), 7.27 (d, J=8 Hz, 2H), 7.47 (d, J=8.16 Hz, 2H), 7.59 (s, 1H), 7.92 (s, 2H). LC-MS (m/z): =535.9 (M+H). HPLC purity: 98.71%.

Example 5

1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone



Preparation 1 for Example 5, Intermediate 1, tert-butyl 3-(4-(3-(3,5-dichloro-4-fluorophenyl)-4,4,4-trifluoro-3-hydroxybutanoyl)phenyl)-3-fluoroazetidine-1-carboxylate, was prepared similarly to Example 1, Intermediate 1, except that 1-(3,5-dichloro-4-fluoro-phenyl)-2,2,2-trifluoro-ethanone was used in place of 1-(3,5-dichlorophenyl)-2,2,2-trifluoro-ethanone. Yield: 7.97 g (93.65.4%). ¹H NMR (400 MHz, CDCl₃) δ: 1.47 (s, 9H), 3.68 (d, J=17.36 Hz, 1H), 3.83 (d, J=17.44 Hz, 1H), 4.17-4.24 (m, 2H), 4.39-4.48 (m, 2H), 5.72 (s, 1H), 7.57 (d, J=6.08 Hz, 2H), 7.63 (d, J=8.44 Hz, 2H), 7.98 (d, J=8.16 Hz, 2H). LC-MS (m/z): =551.8 (M+H).

Preparation 2 for Example 5, Intermediate 2, tert-butyl 3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidine-1-carboxylate, was prepared similarly to Example 1, Intermediate 2, except that tert-butyl 3-(4-(3-(3,5-dichloro-4-fluorophenyl)-4,4,4-trifluoro-3-hydroxybutanoyl)phenyl)-3-fluoroazetidine-1-carboxylate was used in place of 3-{4-[3-(3,5-dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester. Yield: 0.58 g (7.34%). ¹H NMR (400 MHz, CDCl₃) δ: 1.46 (s, 9H), 3.20 (d, J=17.28 Hz, 1H), 3.29-3.33 (m, 2H), 4.14-

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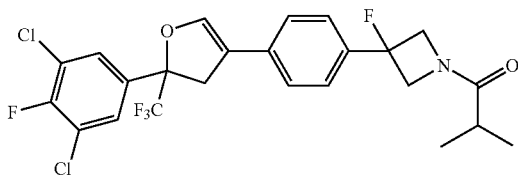
4.21 (m, 2H), 4.33-4.41 (m, 2H), 7.33-7.38 (m, 4H), 7.59 (d, J=6.08 Hz, 2H). LC-MS (m/z): =548.0 (M-H).

Preparation 3 for Example 5, Intermediate 3, 3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-furan-3-yl)phenyl)-3-fluoroazetidine hydrochloride, was prepared similarly to Example 1, Intermediate 3, except that tert-butyl 3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidine-1-carboxylate was used in place of 3-[4-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl]-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester. Yield: 0.45 g (95.74%). ¹H NMR (400 MHz, DMSO-d₆) δ: 3.22 (d, J=17.2 Hz, 1H), 3.68 (d, J=17.16 Hz, 1H), 4.42-4.52 (m, 4H), 7.29 (d, J=8.04 Hz, 2H), 7.52-7.56 (m, 3H), 7.88 (d, J=6.36 Hz, 2H), 9.33 (bs, 1H), 9.74 (bs, 1H). LC-MS (m/z): =449.9 (M+H)

Example 5 was prepared similarly to that of Example 1, except that Example 5, Intermediate 3 was reacted with methane sulfonyl acetic acid. Yield: 0.120 g (46.82%). ¹H NMR (400 MHz, DMSO-d₆) δ: 3.11 (s, 3H), 3.21 (d, J=17.2 Hz, 1H), 3.68 (d, J=17.16 Hz, 1H), 4.24 (s, 2H), 4.34 (d, J=21.68 Hz, 2H), 4.70 (d, J=21.60 Hz, 2H), 7.27 (d, J=8.12 Hz, 2H), 7.46 (d, J=8.28 Hz, 2H), 7.55 (s, 1H), 7.88 (d, J=6.4 Hz, 2H). LC-MS (m/z): =567.8 (M-H). HPLC purity: 99.31%.

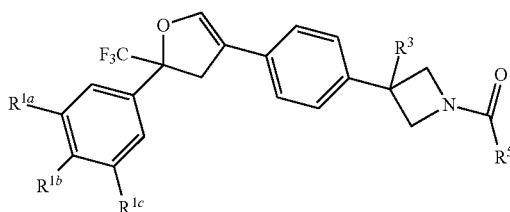
Example 6

1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methyl-propan-1-one



This compound was prepared similarly to Example 5, except that isobutyric acid was used in place of methane sulfonyl acetic acid. Yield: 0.110 g (47.05%). ¹H NMR (400 MHz, CDCl₃) δ: 0.97-1.01 (m, 6H), 2.52-2.55 (m, 1H), 3.20 (d, J=17.24 Hz, 1H), 3.68 (d, J=17.16 Hz, 1H), 4.24 (d, J=22.08 Hz, 2H), 4.60 (d, J=21.88 Hz, 2H), 7.27 (d, J=8 Hz, 2H), 7.47 (d, J=8.16 Hz, 2H), 7.55 (s, 1H), 7.86 (d, J=6.36 Hz, 2H). LC-MS (m/z): =517.8 (M-H). HPLC purity: 98.62%.

In addition to the 6 examples described above, the following examples are also contemplated and can be prepared by the methods and Schemes described herein. The Examples in Table 1 of Formula 2c can be prepared according to the schemes presented herein,



wherein R³ is fluoro (a), hydroxyl (b), or cyano (c).

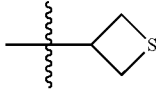
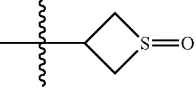
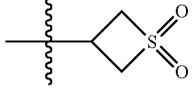
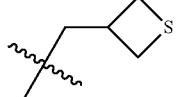
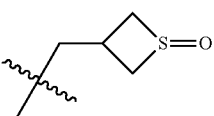
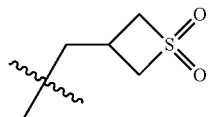
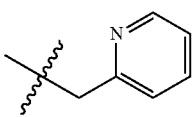
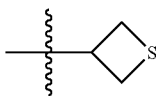
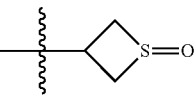
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TABLE 1

Example #	R ^{1a}	R ^{1b}	R ^{1c}	R ⁵
7a,b,c	Cl	Cl	Cl	methyl
8a,b,c	Cl	Cl	Cl	cyclopropyl
9a,b,c	Cl	Cl	Cl	—NHCH ₃
10a,b,c	Cl	Cl	Cl	—NHCH ₂ CH ₃
11a,b,c	Cl	Cl	Cl	—NH-cyclopropyl
12a,b,c	Cl	Cl	Cl	—CH ₂ -cyclopropyl
13b,c	Cl	Cl	Cl	isopropyl
14a,b,c	Cl	Cl	Cl	ethyl
15a,b,c	Cl	Cl	Cl	propyl
16a,b,c	Cl	Cl	Cl	—CH ₂ CN
17a,b,c	Cl	Cl	Cl	—CH ₂ SCH ₃
18a,b,c	Cl	Cl	Cl	—CH ₂ OCH ₃
19a,b,c	Cl	Cl	Cl	cyclobutyl
20a,b,c	Cl	Cl	Cl	—CH ₂ CF ₃
21a,b,c	Cl	Cl	Cl	—NH ₂
22a,b,c	Cl	Cl	Cl	—CH ₂ S(O)CH ₃
23b,c	Cl	Cl	Cl	—CH ₂ S(O) ₂ CH ₃
24a,b,c	Cl	Cl	Cl	—S(O) ₂ CH ₃
25a,b,c	Cl	Cl	Cl	—CH ₂ OH
26a,b,c	Cl	Cl	Cl	n-butyl
27a,b,c	Cl	Cl	Cl	
28a,b,c	Cl	Cl	Cl	
29a,b,c	Cl	Cl	Cl	
30a,b,c	Cl	Cl	Cl	
31a,b,c	Cl	Cl	Cl	
32a,b,c	Cl	Cl	Cl	
33a,b,c	Cl	Cl	Cl	
34a,b,c	Cl	H	Cl	methyl
35a,b,c	Cl	H	Cl	cyclopropyl
36a,b,c	Cl	H	Cl	—NHCH ₃
37a,b,c	Cl	H	Cl	—NHCH ₂ CH ₃
38a,b,c	Cl	H	Cl	—NH-cyclopropyl
39a,b,c	Cl	H	Cl	—CH ₂ -cyclopropyl
40b,c	Cl	H	Cl	isopropyl
41a,b,c	Cl	H	Cl	ethyl
42a,b,c	Cl	H	Cl	propyl
43a,b,c	Cl	H	Cl	—CH ₂ CN
44a,b,c	Cl	H	Cl	—CH ₂ SCH ₃
45a,b,c	Cl	H	Cl	—CH ₂ OCH ₃
46a,b,c	Cl	H	Cl	cyclobutyl
47a,b,c	Cl	H	Cl	—CH ₂ CF ₃
48a,b,c	Cl	H	Cl	—NH ₂

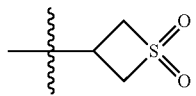
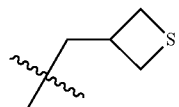
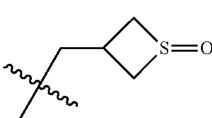
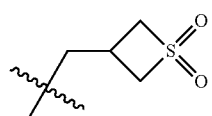
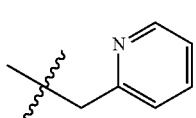
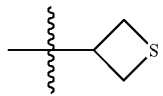
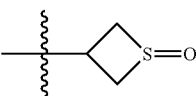
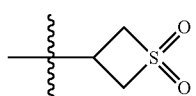
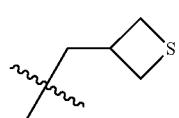
45

TABLE 1-continued

Example #	R ^{1a}	R ^{1b}	R ^{1c}	R ⁵
49a,b,c	Cl	H	Cl	—CH ₂ S(O)CH ₃
50b,c	Cl	H	Cl	—CH ₂ S(O) ₂ CH ₃
51a,b,c	Cl	H	Cl	—S(O) ₂ CH ₃
52a,b,c	Cl	H	Cl	—CH ₂ OH
53a,b,c	Cl	H	Cl	n-butyl
54a,b,c	Cl	H	Cl	
55a,b,c	Cl	H	Cl	
56a,b,c	Cl	H	Cl	
57a,b,c	Cl	H	Cl	
58a,b,c	Cl	H	Cl	
59a,b,c	Cl	H	Cl	
60a,b,c	Cl	H	Cl	
61a,b,c	Cl	F	Cl	—NH ₂
62a,b,c	Cl	F	Cl	methyl
63a,b,c	Cl	F	Cl	cyclopropyl
64a,b,c	Cl	F	Cl	—NHCH ₃
65a,b,c	Cl	F	Cl	—NHCH ₂ CH ₃
66a,b,c	Cl	F	Cl	—NH-cyclopropyl
67a,b,c	Cl	F	Cl	CH ₂ -cyclopropyl
68b,c	Cl	F	Cl	isopropyl
69a,b,c	Cl	F	Cl	ethyl
70a,b,c	Cl	F	Cl	propyl
71a,b,c	Cl	F	Cl	—CH ₂ CN
72a,b,c	Cl	F	Cl	—CH ₂ SCH ₃
73a,b,c	Cl	F	Cl	—CH ₂ OCH ₃
74a,b,c	Cl	F	Cl	cyclobutyl
75a,b,c	Cl	F	Cl	—CH ₂ CF ₃
76a,b,c	Cl	F	Cl	—CH ₂ S(O)CH ₃
77b,c	Cl	F	Cl	—CH ₂ S(O) ₂ CH ₃
78a,b,c	Cl	F	Cl	—S(O) ₂ CH ₃
79a,b,c	Cl	F	Cl	—CH ₂ OH
80a,b,c	Cl	F	Cl	n-butyl
81a,b,c	Cl	F	Cl	
82a,b,c	Cl	F	Cl	

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TABLE 1-continued

Example #	R ^{1a}	R ^{1b}	R ^{1c}	R ⁵
83a,b,c	Cl	F	Cl	
84a,b,c	Cl	F	Cl	
85a,b,c	Cl	F	Cl	
86a,b,c	Cl	F	Cl	
87a,b,c	Cl	F	Cl	
88a,b,c	Cl	H	CF ₃	—NH ₂
89a,b,c	Cl	H	CF ₃	methyl
90a,b,c	Cl	H	CF ₃	cyclopropyl
91a,b,c	Cl	H	CF ₃	—NHCH ₃
92a,b,c	Cl	H	CF ₃	—NHCH ₂ CH ₃
93a,b,c	Cl	H	CF ₃	—NH-cyclopropyl
94a,b,c	Cl	H	CF ₃	CH ₂ -cyclopropyl
95a,b,c	Cl	H	CF ₃	isopropyl
96a,b,c	Cl	H	CF ₃	ethyl
97a,b,c	Cl	H	CF ₃	propyl
98a,b,c	Cl	H	CF ₃	—CH ₂ CN
99a,b,c	Cl	H	CF ₃	—CH ₂ SCH ₃
100a,b,c	Cl	H	CF ₃	—CH ₂ OCH ₃
101a,b,c	Cl	H	CF ₃	cyclobutyl
102a,b,c	Cl	H	CF ₃	—CH ₂ CF ₃
103a,b,c	Cl	H	CF ₃	—CH ₂ S(O)CH ₃
104a,b,c	Cl	H	CF ₃	—CH ₂ S(O) ₂ CH ₃
105a,b,c	Cl	H	CF ₃	—S(O) ₂ CH ₃
106a,b,c	Cl	H	CF ₃	—CH ₂ OH
107a,b,c	Cl	H	CF ₃	
108a,b,c	Cl	H	CF ₃	
109a,b,c	Cl	H	CF ₃	
110a,b,c	Cl	H	CF ₃	

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TABLE 1-continued

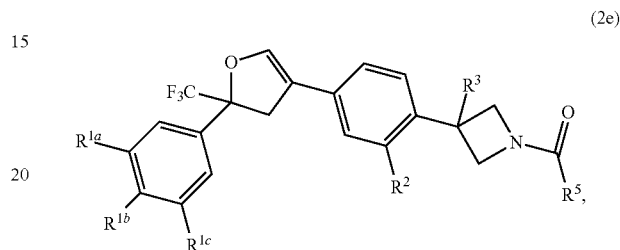
Example #	R ^{1a}	R ^{1b}	R ^{1c}	R ⁵
111a,b,c	Cl	H	CF ₃	
112a,b,c	Cl	H	CF ₃	
113a,b,c	Cl	H	CF ₃	
114a,b,c	Cl	H	Cl	n-butyl
115a,b,c	Cl	Cl	CF ₃	—NH ₂
116a,b,c	Cl	Cl	CF ₃	methyl
117a,b,c	Cl	Cl	CF ₃	cyclopropyl
118a,b,c	Cl	Cl	CF ₃	—NHCH ₃
119a,b,c	Cl	Cl	CF ₃	—NHCH ₂ CH ₃
120a,b,c	Cl	Cl	CF ₃	—NH-cyclopropyl
121a,b,c	Cl	Cl	CF ₃	CH ₂ -cyclopropyl
122a,b,c	Cl	Cl	CF ₃	isopropyl
123a,b,c	Cl	Cl	CF ₃	ethyl
124a,b,c	Cl	Cl	CF ₃	propyl
125a,b,c	Cl	Cl	CF ₃	—CH ₂ CN
126a,b,c	Cl	Cl	CF ₃	—CH ₂ SCH ₃
127a,b,c	Cl	Cl	CF ₃	—CH ₂ OCH ₃
128a,b,c	Cl	Cl	CF ₃	cyclobutyl
129a,b,c	Cl	Cl	CF ₃	—CH ₂ SCF ₃
130a,b,c	Cl	Cl	CF ₃	—CH ₂ S(O)CH ₃
131a,b,c	Cl	Cl	CF ₃	—CH ₂ S(O) ₂ CH ₃
132a,b,c	Cl	Cl	CF ₃	—S(O) ₂ CH ₃
133a,b,c	Cl	Cl	CF ₃	—CH ₂ OH
134a,b,c	Cl	Cl	CF ₃	n-butyl
135a,b,c	Cl	Cl	CF ₃	
136a,b,c	Cl	Cl	CF ₃	
137a,b,c	Cl	Cl	CF ₃	
138a,b,c	Cl	Cl	CF ₃	
139a,b,c	Cl	Cl	CF ₃	
140a,b,c	Cl	Cl	CF ₃	

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TABLE 1-continued

Example #	R ^{1a}	R ^{1b}	R ^{1c}	R ⁵
141a,b,c	Cl	Cl	CF ₃	

10 In addition to the compounds of Table 1 of Formula 2c, similar compounds can be prepared from Formula (2e)



25 wherein R² is selected from chloro, bromo, cyano, and fluoro.

Biological Assays

The biological activity of the compounds of the present invention can be tested against fleas, ticks, flies, and or sea lice using the test methods described below.

Horn Fly (*Haematobia irritans*) Feed Assay

Formula (1) compounds can be dissolved in DMSO and aliquots added to citrated bovine blood in a membrane covered Petri dish. Approximately ten horn flies are placed onto each Petri dish and covered. The flies are allowed to feed on the treated blood cell. Flies are held at approximately 80° F. with a minimum of approximately 50% relative humidity. Flies are examined for knockdown and mortality at approximately 2 and 24 hours. Endpoint data is recorded as a lethal dose 90% (LD⁹⁰) in µg/mL.

Stable Fly (*Stomoxys calcitrans*) Topical Assay

Formula (1) compounds can be dissolved in acetone, and 1 µL of the solution placed on the thorax of an anesthetized fly (n=10). The flies are allowed to recover, and are incubated for 24 hours at room temperature. Flies are examined for knockdown and mortality at 2 and 24 hours. Endpoint data is recorded as lethal dose 90% (LD⁹⁰) in µg/fly.

Flea (*Ctenocephalides felis*) Membrane Feed Assay-Adult

Formula (1) compounds were dissolved in DMSO and aliquots added to citrated bovine blood in a membrane covered Petri dish pre-warmed to 37° C. Feeding tubes containing approximately 30-35 adult fleas are placed onto the Petri dishes. The fleas are allowed to feed for approximately 2 hours. Fleas are observed for knockdown and/or death at approximately 2 and 24 hours. Endpoint data is recorded as a lethal dose 90% (LD⁹⁰) in µg/mL. Examples 1-6 had LD⁹⁰ values >3 µg/mL.

Soft Tick (*Ornithodoros turicata*) Blood Feed Assay

Formula (1) compounds can be dissolved in dimethylsulfoxide (DMSO) and aliquots added to citrated bovine blood in a membrane covered Petri dish. The Petri dish is placed on a warming tray. Approximately 5 nymph stage ticks are placed onto the membrane, covered, and left to feed. Fed ticks are removed and placed into a Petri dish with sand. Fed ticks are observed at approximately 24, 48 and 72 hours for paralysis

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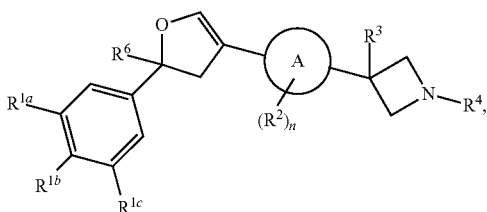
and/or death. Endpoint data is recorded as an ED¹⁰⁰ and/or an LD¹⁰⁰ in µg/mL. Positive control is fipronil and DMSO for the negative control.

Copepod (*Lepeophtheirus salmonis*) BioAssay

Formula (1) compounds can be dissolved in sea water. Negative control is sea water and positive control is emamectin benzoate. Ten pre-adult/adult salmon lice are exposed for 24 hours. Lice are monitored for motility and endpoint data is recorded as an Effective Concentration 100% (EC¹⁰⁰) based on immotility.

We claim:

1. A compound of Formula (1)



wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a}, R^{1b}, and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₀-C₃alkylC₃-C₆cycloalkyl, C₁-C₆haloalkoxy, —C(O)NH₂, —SF₅, or —S(O)_pR;

R² is halo, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, nitro, hydroxyl, —C(O)NR^aR^b, C₂-C₆alkenyl, C₂-C₆alkynyl, —S(O)_pR, or —OR;

R³ is hydrogen, halo, hydroxyl, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₀-C₃alkylC₃-C₆cycloalkyl, —C(O)NH₂, nitro, —SC(O)R, —C(O)NR^aR^b, C₀-C₃alkylNR^aR⁴, —NR^aNR^bR⁴, —NR^aOR^b, —ONR^aR^b, N₃, —NHR⁴, —OR, or —S(O)_pR;

R⁴ is hydrogen, C₁-C₆alkyl, C₀-C₆alkylC₃-C₆cycloalkyl, —C(O)R⁵, —C(S)R⁵, —C(O)NR^aR⁵, —C(O)C(O)NR^aR⁵, —S(O)_pR^c, —S(O)₂NR^aR⁵, —C(NR⁷)R⁵, —C(NR⁷)NR^aR⁵, C₀-C₆alkylphenyl, C₀-C₆alkylheteroaryl, or C₀-C₆alkylheterocycle;

R⁵ is hydrogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₀-C₆alkylC₃-C₆cycloalkyl, C₀-C₆alkylphenyl, C₀-C₆alkylheteroaryl, or C₀-C₆alkyl heterocycle;

R⁶ is cyano, C₁-C₆haloalkyl, —C(O)NR^aR^b, C₂-C₆alkenyl, C₂-C₆alkynyl, C₂-C₆haloalkenyl, or C₂-C₆haloalkynyl;

R⁷ is hydrogen, C₁-C₆alkyl, hydroxyl, cyano, nitro, —S(O)_pR^c, or C₁-C₆alkoxy;

R is C₁-C₆alkyl or C₃-C₆cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C₁-C₆alkyl, or C₀-C₃alkylC₃-C₆cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, C₀-C₃alkylphenyl, C₀-C₃alkylheteroaryl, or C₀-C₃alkylheterocycle, each optionally substituted, where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or —S(O)_pR;

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R^c is C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆haloalkylC₃-C₆cycloalkyl, C₀-C₃alkylC₃-C₆cycloalkyl, C₀-C₃alkylphenyl, C₀-C₃alkylheteroaryl, or C₀-C₃alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆haloalkyl, —S(O)_pR, —SH, —S(O)_pNR^aR^b, —NR^aR^b, —NR^aC(O)R^b, —SC(O)R^b, —SCN, or —C(O)NR^aR^b;

each of R⁴ and R⁵ C₁-C₆alkyl or C₀-C₆alkylC₃-C₆cycloalkyl can be optionally and independently substituted by at least one substituent selected from C₁-C₆alkyl, C₁-C₆hydroxyalkyl, cyano, halo, hydroxyl, oxo, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆haloalkyl, —S(O)_pR^c, —SH, —S(O)_pNR^aR^b, —NR^aR^b, —NR^aC(O)R^b, —SC(O)R^b, —SCN, or —C(O)NR^aR^b; and

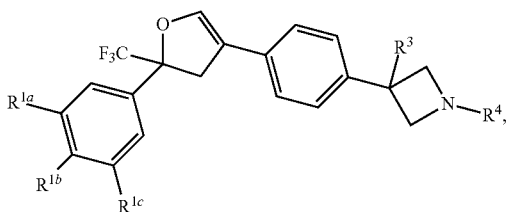
wherein R⁴ and R⁵ C₀-C₆alkylphenyl, C₀-C₆alkylheteroaryl, or C₀-C₆alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from C₁-C₆alkyl, C₁-C₆hydroxyalkyl, cyano, halo, oxo, —S, —NR⁷, hydroxyl, C₁-C₆alkoxy, C₁-C₆alkyl, C₁-C₆haloalkyl, —SH, —S(O)_pR, and C₁-C₆haloalkoxy;

n is the integer 0, 1, or 2, and when n is 2, each R² may be identical or different from each other; and

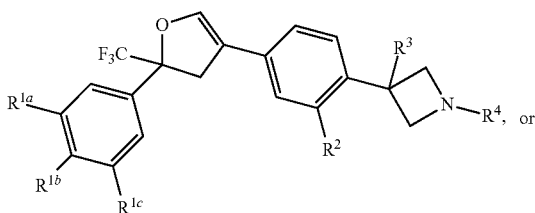
p is the integer 0, 1, or 2;

stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

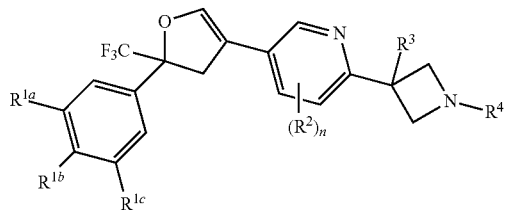
2. The compound of claim 1 having Formula (2a), (2b), or (6a)



(2a)



(2b)



(6a)

wherein

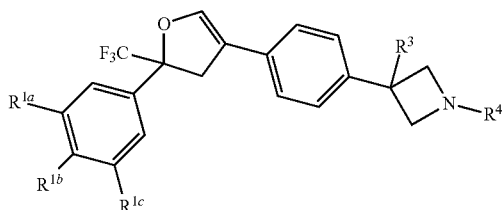
R^{1a}, R^{1b}, and R^{1c} are each independently selected from hydrogen, halo, hydroxyl, and C₁-C₆ haloalkyl;

R² is halo, cyano, hydroxyl, —C(O)NR^aR^b, or —OR; and R³ is hydrogen, halo, hydroxyl, N₃, or cyano;

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stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

3. The compound of claim 2 having Formula (2a)



wherein

R^{1a} , R^{1b} , and R^{1c} are each independently selected from hydrogen, halo, and C_1 - C_6 haloalkyl; and

R^3 is hydrogen, halo, hydroxyl, or cyano;

stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

4. The compound of claim 3 wherein

R^4 is $-C(O)R^5$, $-C(O)NR^aR^5$, $-S(O)_pR^c$, $-C(S)R^5$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$; or $-C(NR^7)NR^aR^5$;

stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

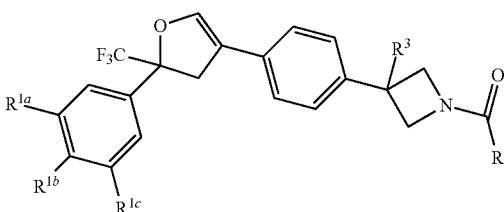
5. The compound of claim 4 wherein

R^{1a} , R^{1b} , and R^{1c} are each independently selected from hydrogen, chloro, fluoro, bromo, and C_1 - C_6 haloalkyl; and

R^4 is $-C(O)R^5$, $-C(O)NR^aR^5$, or $-C(NR^7)R^5$;

stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

6. The compound of claim 5 of Formula (2a) having Formula (2c)



wherein

R^{1a} , R^{1b} , and R^{1c} are each independently selected from hydrogen, chloro, fluoro, and C_1 - C_6 haloalkyl;

stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

7. A compound of claim 6 selected from the group selected from:

1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;

1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;

1-(3-(4-(5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl)-phenyl)-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone;

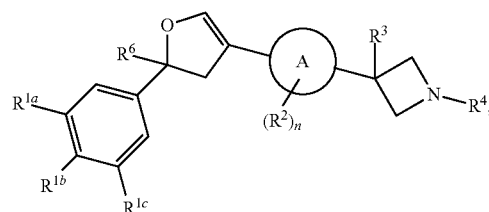
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1-(3-Fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-di-hydro-furan-3-yl]-phenyl}-azetidin-1-yl)-2-methyl-propan-1-one;

1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone; and

1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methyl-propan-1-one, stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

8. A pharmaceutical or veterinary composition comprising a therapeutic amount of a compound of Formula (1)



wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a} , R^{1b} , and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_0 - C_3 alkyl/ C_3 - C_6 cycloalkyl, C_1 - C_6 haloalkoxy, $-C(O)NH_2$, $-SF_5$, or $-S(O)_pR$;

R^2 is halo, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, nitro, hydroxyl, $-C(O)NR^aR^b$, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $-S(O)_pR$, or $-OR$;

R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl/ C_3 - C_6 cycloalkyl, $-C(O)NH_2$, nitro, $-SC(O)R$, $-C(O)NR^aR^b$, C_0 - C_3 alkyl/ C_3 - C_6 cycloalkyl, $-NR^aNR^bR^c$, $-NR^aOR^b$, $-ONR^aR^b$, N_3 , $-NHR^4$, $-OR$, or $-S(O)_pR$;

R^4 is hydrogen, C_1 - C_6 alkyl, C_0 - C_3 alkyl/ C_3 - C_6 cycloalkyl, $-C(O)R^5$, $-C(S)R^5$, $-C(O)NR^aR^5$, $-C(O)C(O)NR^aR^5$, $-S(O)_pR^c$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$, $-C(NR^7)NR^aR^5$, C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle;

R^5 is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_0 - C_6 alkyl/ C_3 - C_6 cycloalkyl, C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle;

R^6 is cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-C(O)NR^aR^b$, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_2 - C_6 haloalkenyl, or C_2 - C_6 haloalkynyl;

R^7 is hydrogen, C_1 - C_6 alkyl, hydroxyl, cyano, nitro, $-S(O)_pR^c$, or C_1 - C_6 alkoxy;

R is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C_1 - C_6 alkyl, or C_0 - C_3 alkyl/ C_3 - C_6 cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, C_0 - C_3 alkylheteroaryl, or C_0 - C_3 alkylheterocycle, each optionally substituted,

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where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or $-\text{S}(\text{O})_p\text{R}$;

R^c is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkyl $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_0\text{-C}_3$ alkyl $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_0\text{-C}_3$ alkylphenyl, $\text{C}_0\text{-C}_3$ alkylheteroaryl, or $\text{C}_0\text{-C}_3$ alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{S}(\text{O})_p\text{R}$, $-\text{SH}$, $-\text{S}(\text{O})_p\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{R}^b$, $-\text{SC}(\text{O})\text{R}^b$, $-\text{SCN}$, or $-\text{C}(\text{O})\text{NR}^a\text{R}^b$;

each of R^4 and R^5 $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_0\text{-C}_6$ alkyl $\text{C}_3\text{-C}_6$ cycloalkyl can be optionally and independently substituted by at least one substituent selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, cyano, halo, hydroxyl, oxo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{S}(\text{O})_p\text{R}^c$, $-\text{SH}$, $-\text{S}(\text{O})_p\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{R}^b$, $-\text{SC}(\text{O})\text{R}^c$, $-\text{SCN}$, or $-\text{C}(\text{O})\text{NR}^a\text{R}^b$; and

wherein R^4 and R^5 $\text{C}_0\text{-C}_6$ alkylphenyl, $\text{C}_0\text{-C}_6$ alkylheteroaryl, or $\text{C}_0\text{-C}_6$ alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, cyano, halo, oxo, $=\text{S}$, $=\text{NR}^7$, hydroxyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{SH}$, $-\text{S}(\text{O})_p\text{R}$, and $\text{C}_1\text{-C}_6$ haloalkoxy;

n is the integer 0, 1, or 2, and when n is 2, each R^2 may be identical or different from each other; and

p is the integer 0, 1, or 2;

stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

9. The pharmaceutical or veterinary composition of claim 8 further comprising a pharmaceutically or veterinarily acceptable excipient, diluent, or carrier.

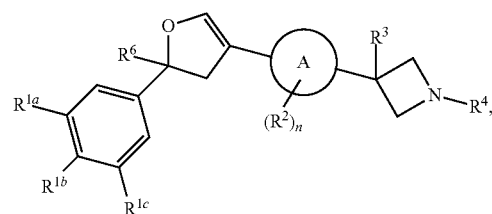
10. The pharmaceutical or veterinary composition of claim 9 further comprising at least one additional veterinary agent.

11. The pharmaceutical or veterinary composition of claim 10 wherein said additional veterinary agent is selected from the group consisting of abamectin, ivermectin, avermectin, moxidectin, emamectin, eprinomectin, selamectin, doramectin, nemadectin, albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, oxfenbendazole, oxi-bendazole, parbendazole, tetramisole, levamisole, pyrantel pamoate, oxantel, morantel, indoxacarb, closantel, triclabendazole, clorsulon, refoxanide, niclosamide, praziquantel, epsiprantel, 2-desoxoparahequamide, pyripole, pyrafluprole, lufenuron, spiromesifen, tebufenozide, spinosad, spinetoram, imidacloprid, dinotefuran, metaflumizone, thibendiamide, chlorantraniliprole, indoxacarb, pyridalyl, pyrimidifen, pyri-fluquinazon, milbemycin oxime, milbemycin, DEET, demiditraz, amitraz, fipronil, methoprene, hydroprene, nov-aluron, lufenuron, permethrin, and pyrethrin, or mixtures thereof.

12. The pharmaceutical or veterinary composition of claim 11 wherein said additional veterinary agent is milbemycin oxime or moxidectin.

13. A method for the treatment of an animal with a parasitic infection or infestation comprising administering to said animal in need thereof an effective amount of a compound of Formula (1)

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wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a} , R^{1b} , and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_0\text{-C}_3$ alkyl $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $-\text{C}(\text{O})\text{NH}_2$, $-\text{SF}_5$, or $-\text{S}(\text{O})_p\text{R}$;

R^2 is halo, cyano, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, nitro, hydroxyl, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $-\text{S}(\text{O})_p\text{R}$, or $-\text{OR}$;

R^3 is hydrogen, halo, hydroxyl, cyano, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_0\text{-C}_3$ alkyl $\text{C}_3\text{-C}_6$ cycloalkyl, $-\text{C}(\text{O})\text{NH}_2$, nitro, $-\text{SC}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{C}_0\text{-C}_3$ alkyl NR^aR^4 , $-\text{NR}^a\text{NR}^b\text{R}^4$, $-\text{NR}^a\text{OR}^b$, $-\text{ONR}^a\text{R}^b$, N_3 , $-\text{NHR}^4$, $-\text{OR}$, or $-\text{S}(\text{O})_p\text{R}$;

R^4 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_0\text{-C}_6$ alkyl $\text{C}_3\text{-C}_6$ cycloalkyl, $-\text{C}(\text{O})\text{R}^5$, $-\text{C}(\text{S})\text{R}^5$, $-\text{C}(\text{O})\text{NR}^a\text{R}^5$, $-\text{C}(\text{O})\text{C}(\text{O})\text{NR}^a\text{R}^5$, $-\text{S}(\text{O})_p\text{R}^c$, $-\text{S}(\text{O})_2\text{NR}^a\text{R}^5$, $-\text{C}(\text{NR}^7)\text{R}^5$, $-\text{C}(\text{NR}^7)\text{NR}^a\text{R}^5$, $\text{C}_0\text{-C}_6$ alkylphenyl, $\text{C}_0\text{-C}_6$ alkylheteroaryl, or $\text{C}_0\text{-C}_6$ alkylheterocycle;

R^5 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_0\text{-C}_6$ alkyl $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_0\text{-C}_6$ alkylphenyl, $\text{C}_0\text{-C}_6$ alkylheteroaryl, or $\text{C}_0\text{-C}_6$ alkylheterocycle;

R^6 is cyano, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_2\text{-C}_6$ haloalkenyl, or $\text{C}_2\text{-C}_6$ haloalkynyl;

R^7 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, hydroxyl, cyano, nitro, $-\text{S}(\text{O})_p\text{R}^c$, or $\text{C}_1\text{-C}_6$ alkoxy;

R is $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_0\text{-C}_3$ alkyl $\text{C}_3\text{-C}_6$ cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_0\text{-C}_3$ alkylphenyl, $\text{C}_0\text{-C}_3$ alkylheteroaryl, or $\text{C}_0\text{-C}_3$ alkylheterocycle, each optionally substituted, where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or $-\text{S}(\text{O})_p\text{R}$;

R^c is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkyl $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_0\text{-C}_3$ alkyl $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_0\text{-C}_3$ alkylphenyl, $\text{C}_0\text{-C}_3$ alkylheteroaryl, or $\text{C}_0\text{-C}_3$ alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{S}(\text{O})_p\text{R}$, $-\text{SH}$, $-\text{S}(\text{O})_p\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{R}^b$, $-\text{SC}(\text{O})\text{R}^b$, $-\text{SCN}$, or $-\text{C}(\text{O})\text{NR}^a\text{R}^b$;

each of R^4 and R^5 $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_0\text{-C}_6$ alkyl $\text{C}_3\text{-C}_6$ cycloalkyl can be optionally and independently substituted by at least one substituent selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, cyano, halo, hydroxyl, oxo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy,

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C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, $-S(O)_pR^b$,
 $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$,
 $-SC(O)R^c$, $-SCN$, or $-C(O)NR^aR^b$; and
 wherein R^4 and R^5 C_0 - C_6 alkylphenyl,
 C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle moi- 5
 ety can be further optionally substituted with at least
 one substituent selected from C_1 - C_6 alkyl,
 C_1 - C_6 hydroxyalkyl, cyano, halo, oxo, $=S$, $=NR^7$,
 hydroxyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl,
 $-SH$, $-S(O)_pR$, and C_1 - C_6 haloalkoxy; 10
 n is the integer 0, 1, or 2, and when n is 2, each R^2 may
 be identical or different from each other; and
 p is the integer 0, 1, or 2;
 stereoisomers thereof, and pharmaceutically or veteri-
 narily acceptable salts thereof. 15

14. The method of claim 13 wherein the compound of
 Formula (1) is administered to the animal topically, orally, or
 by injection.

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